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RHEUMATOLOGY

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RHEUMATOLOGY

Derived from Harrison's Principles of Internal Medicine, 19th Edition

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PREFACE

Welcome to the fourth edition of Harrison's Rheumatology. T is sectional volume, which is comprised of the rheumatology and immunology chapters contained in the 19th edition of Harrison's Principles *of* Internal Medicine, was originally introduced with the goal of providing knowledge to enhance the care of patients with rheumatic diseases and in recognition of the importance of the field of rheumatology to the practice of internal medicine. With the rapid changes that have occurred throughout the practice of medicine, the significance of these original foundations to patient care have become even more significant.

Rheumatic diseases occur throughout the spectrum of life. T is ranges from illnesses such as juvenile idiopathic arthritis, systemic lupus erthyematosus, inflammatory myositis, and Kawasaki disease that can occur in childhood but have a lasting impact into adulthood to diseases that can occur over the course of years. T is includes diverse illnesses such as osteoarthritis, rheumatoid arthritis, spondyloarthritides, Sjögren's syndrome, systemic sclerosis, crystalline arthropathies, regional musculoskeletal diseases, and the vasculitic diseases. As many of these may increase with age, the ability to recognize and treat rheumatic diseases has carried an increasing presence within the practice of medicine.

Rheumatology and immunology exemplify many of the exciting qualities of internal medicine. T is includes rapid scientific growth, diagnostic challenges, and therapeutic advancements. Most significantly though is the potential that exists to provide a meaningful difference for our patients and their families. Over the years we have seen how the advancements in rheumatology and immunology have had a positive impact on the lives of our patients, reminding us all of why a life dedicated to internal medicine remains such important and gratifying career decision. As our science rapidly expands, our patients look to the human face of physicians in providing knowledge and guidance regarding their complex medical decisions. T e partnership that exists between a dedication to better understanding the causes and treatment of disease together with the physician-patient relationship is what embodies internal medicine and rheumatology/immunology.

With each edition of Harrison's Rheumatology we have seen the introduction of novel scientific insights and how these findings have the ability to improve both the quality and duration of life. We look ahead with great anticipation for what new advances in rheumatology will bring. While the primary purpose of Harrison's Rheumatology is to provide the most updated information about the rheumatic diseases, we also hope that it will inspire a clinical curiosity and drive to understand more about this dynamic field of internal medicine.

T e publication of this sectional would not be possible without the contributions and expertise of our dedicated authors. We also want to recognize the many individuals who conduct the basic, translational, and clinical research in rheumatology and immunology whose contributions have lead to the advancements described in these pages. It is the continued hope of the Editors that Harrison's Rheumatology that this information will increase your appreciation of this challenging and fulfilling specialty. Most importantly though is that we hope that this knowledge will benefit your ability to provide skilled care that will enhance the lives of patients.

Anthony S. Fauci, MD
Carol A. Langford, MD, MHS

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-259-64288-3.



T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.



T e genetic icons identify a clinical issue with an explicit genetic relationship.

SECTION I

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

CHAPTER 1

INTRODUCTION TO THE IMMUNE SYSTEM

Barton F. Haynes ■ Kelly A. Soderberg ■ Anthony S. Fauci

DEFINITIONS

- Adaptive immune system—recently evolved system of immune responses mediated by T and B lymphocytes. Immune responses by these cells are based on specific antigen recognition by clonotypic receptors that are products of genes that rearrange during development and throughout the life of the organism. Additional cells of the adaptive immune system include various types of antigen-presenting cells.
- Antibody—B cell–produced molecules encoded by genes that re-arrange during B cell development consisting of immunoglobulin heavy and light chains that together form the central component of the B cell receptor for antigen. Antibody can exist as B cell–surface antigen-recognition molecules or as secreted molecules in plasma and other body fluids.
- Antigens—foreign or self-molecules that are recognized by the adaptive and innate immune systems resulting in immune cell triggering, T cell activation, and/or B cell antibody production.
- Antimicrobial peptides—small peptides <100 amino acids in length that are produced by cells of the innate immune system and have anti-infectious agent activity.
- Apoptosis—the process of programmed cell death whereby signaling through various "death receptors" on the surface of cells (e.g., tumor necrosis factor [TNF] receptors, CD95) leads to a signaling cascade that involves activation of the caspase family of molecules and leads to DNA cleavage and cell death. Apoptosis, which does not lead to induction of inordinate inflammation, is to be contrasted with cell necrosis, which does lead to induction of inflammatory responses.
- Autoimmune diseases—diseases such as systemic lupus erythematosus and rheumatoid arthritis in which cells of the adaptive immune system such as autoreactive T and B cells become overreactive and produce self-reactive T cell and antibody responses.
- Autoinflammatory diseases—hereditary disorders such as hereditary periodic fevers (HPFs) characterized by recurrent episodes of severe inflammation and fever due to mutations in controls of the innate inflammatory response, i.e., the inflammasome (see below and **Table 1-6**). Patients with HPFs also have rashes and serosal and joint inflammation, and some can have neurologic symptoms. Autoinflammatory diseases are different from autoimmune diseases in that evidence for activation of adaptive immune cells such as autoreactive B cells is not present.
- B cell receptor for antigen—complex of surface molecules that rearrange during postnatal B cell development, made up of surface immunoglobulin (Ig) and associated Ig αβ chain molecules that recognize nominal antigen via Ig heavy- and light-chain variable regions, and signal the B cell to terminally differentiate to make antigen-specific antibody.
- B lymphocytes—bone marrow-derived or bursal-equivalent lymphocytes that express surface immunoglobulin (the B cell receptor for antigen) and secrete specific antibody after interaction with antigen.
- CD classification of human lymphocyte differentiation antigens—the development of monoclonal antibody technology led to the discovery of a large number of new leukocyte surface molecules. In 1982, the First International Workshop on Leukocyte Differentiation Antigens was held to establish a nomenclature for cell-surface molecules of human leukocytes. From this and subsequent leukocyte differentiation workshops has come the cluster of differentiation (CD) classification of leukocyte antigens.
- Chemokines—soluble molecules that direct and determine immune cell movement and circulation pathways.

- Complement—cascading series of plasma enzymes and effector proteins whose function is to lyse pathogens and/or target them to be phagocytized by neutrophils and monocyte/macrophage lineage cells of the reticuloendothelial system.
- Co-stimulatory molecules—molecules of antigen-presenting cells (such as B7-1 and B7-2 or CD40) that lead to T cell activation when bound by ligands on activated T cells (such as CD28 or CD40 ligand).
- Cytokines—soluble proteins that interact with specific cellular receptors that are involved in the regulation of the growth and activation of immune cells and mediate normal and pathologic inflammatory and immune responses.
- Dendritic cells—myeloid and/or lymphoid lineage antigen-presenting cells of the adaptive immune system. Immature dendritic cells, or dendritic cell precursors, are key components of the innate immune system by responding to infections with production of high levels of cytokines. Dendritic cells are key initiators both of innate immune responses via cytokine production and of adaptive immune responses via presentation of antigen to T lymphocytes.
- Ig Fc receptors—receptors found on the surface of certain cells including B cells, natural killer cells, macrophages, neutrophils, and mast cells. Fc receptors bind to antibodies that have attached to invading pathogen-infected cells. They stimulate cytotoxic cells to destroy microbe-infected cells through a mechanism known as antibody-dependent cell-mediated cytotoxicity (ADCC). Examples of important Fc receptors include CD16 (FcγRIIIa), CD23 (FcεR), CD32 (FcγRII), CD64 (FcγRI), and CD89 (FcαR).
- In*fl*ammasome—large cytoplasmic complexes of intracellular proteins that link the sensing of microbial products and cellular stress to the proteolytic activation of interleukin (IL)-1β and IL-18 inflammatory cytokines. Activation of molecules in the inflammasome is a key step in the response of the innate immune system for intracellular recognition of microbial and other danger signals in both health and pathologic states.
- Innate immune system—ancient immune recognition system of host cells bearing germline-encoded pattern recognition receptors that recognize pathogens and trigger a variety of mechanisms of pathogen elimination. Cells of the innate immune system include natural killer cell lymphocytes, monocytes/macrophages, dendritic cells, neutrophils, basophils, eosinophils, tissue mast cells, and epithelial cells.
- Large granular lymphocytes—lymphocytes of the innate immune system with azurophilic cytotoxic granules that have natural killer cell activity capable of killing foreign and host cells with few or no self-major histocompatibility complex (MHC) class I molecules.
- Natural killer (NK) cells—large granular lymphocytes that kill target cells expressing few or no human leukocyte antigen (HLA) class I molecules, such as malignantly transformed cells and virally infected cells. NK cells express receptors that inhibit killer cell function when self-MHC class I is present.
- NK T cells—innate-like lymphocytes that use an invariant T cell receptor (TCR)-α chain combined with a limited set of TCR-β chains and coexpress receptors commonly found on NK cells. NK T cells recognize lipid antigens of bacterial, viral, fungal, and protozoal infectious agents.
- Pathogen-associated molecular patterns (PAMPs)—Invariant molecular structures expressed by large groups of microorganisms that are recognized by host cellular pattern recognition receptors in the mediation of innate immunity.
- Pattern recognition receptors (PRRs)—germline-encoded receptors expressed by cells of the innate immune system that recognize PAMPs.
- Polyreactive natural antibodies—preexisting low-affinity antibodies produced by B cells that cross-react with multiple antigens and are available at the time of infection to bind to and coat the invading pathogen and harness innate responses to slow the infection until an adaptive high-affinity protective antibody response can be made.
- T cell exhaustion—state of T cells when the persistence of antigen disrupts memory T cell function, resulting in defects in memory T cell responses. Most frequently occurs in malignancies and in chronic viral infections such as HIV-1 and hepatitis C.
- T cell receptor (TCR) *f*or antigen—complex of surface molecules that rearrange during postnatal T cell development made up of clonotypic TCR-α and -β chains that are associated with the CD3 complex composed of invariant γ, δ, ε, ζ, and η chains. TCR-α and -β chains recognize peptide fragments of protein antigen physically bound in antigen-presenting cell MHC class I or II molecules, leading to signaling via the CD3 complex to mediate effector functions.
- T *f*ollicular helper T cells (T*fh*)—CD4 T cells in B cell follicle germinal centers that produce IL-4 and IL-21 and drive B cell development and affinity maturation in peripheral lymphoid tissues such as lymph node and spleen.
- T_H17 T cells—CD4 T cells that secrete IL-17, IL-22, and IL-26 and play roles in autoimmune inflammatory disorders as well as defend against bacterial and fungal pathogens.
- T lymphocytes—thymus-derived lymphocytes that mediate adaptive cellular immune responses including T helper, T regulatory, and cytotoxic T lymphocyte effector cell functions.
- Tolerance—B and T cell nonresponsiveness to antigens that results from encounter with foreign or

self-antigens by B and T lymphocytes in the absence of expression of antigen-presenting cell co-stimulatory molecules. Tolerance to antigens may be induced and maintained by multiple mechanisms either centrally (in the thymus for T cells or bone marrow for B cells) or peripherally at sites throughout the peripheral immune system.

INTRODUCTION

The human immune system has evolved over millions of years from both invertebrate and vertebrate organisms to develop sophisticated defense mechanisms to protect the host from microbes and their virulence factors. The normal immune system has three key properties: a highly diverse repertoire of antigen receptors that enables recognition of a nearly infinite range of pathogens; immune memory, to mount rapid recall immune responses; and immunologic tolerance, to avoid immune damage to normal self-tissues. From invertebrates, humans have inherited the innate immune system, an ancient defense system that uses germline-encoded proteins to recognize pathogens. Cells of the innate immune system, such as macrophages, dendritic cells, and NK lymphocytes, recognize PAMPs that are highly conserved among many microbes and use a diverse set of PRR molecules. Important components of the recognition of microbes by the innate immune system include recognition by germline-encoded host molecules, recognition of key microbe virulence factors but not recognition of self-molecules, and nonrecognition of benign foreign molecules or microbes. Upon contact with pathogens, macrophages and NK cells may kill pathogens directly or, in concert with dendritic cells, may activate a series of events that both slow the infection and recruit the more recently evolved arm of the human immune system, the adaptive immune system.

Adaptive immunity is found only in vertebrates and is based on the generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of specifically recognizing diverse antigens of the myriad infectious agents in the environment. Coupled with finely tuned specific recognition mechanisms that maintain tolerance (nonreactivity) to self-antigens, T and B lymphocytes bring both specificity and immune memory to vertebrate host defenses.

This chapter describes the cellular components, key molecules **(Table 1-1)**, and mechanisms that make up the innate and adaptive immune systems and describes how adaptive immunity is recruited to the defense of the host by innate immune responses. An appreciation of the cellular and molecular bases of innate and adaptive immune responses is critical to understanding the pathogenesis of inflammatory, autoimmune, infectious, and immunodeficiency diseases.

TABLE 1-1

HUMAN LEUKOCYTE SURFACE ANTIGENS—THE CD CLASSIFICATION OF LEUKOCYTE DIFFERENTIATION ANTIGENS

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, KDA	DISTRIBUTION	LIGAND(S)	FUNCTION
CD1a (T6, HTA-1)	Ig	49	CD, cortical thymocytes, Langerhans type of DCs	TCRγδ T cells	CD1 molecules present lipid antigens of intracellular bacteria such as Mycobacterium leprae and M. tuberculosis to TCRγδ T cells
CD1b	Ig	45	CD, cortical thymocytes, Langerhans type of DCs	TCRγδ T cells	
CD1c	Ig	43	DC, cortical thymocytes, subset of B cells, Langerhans type of DCs	TCRγδ T cells	
CD1d	Ig	37	Cortical thymocytes, intestinal epithelium, Langerhans type of DCs	TCRγδ T cells	
CD2 (T12, LFA-2)	Ig	50	T, NK	CD58, CD48, CD59, CD15	Alternative T cell activation, T cell anergy, T cell cytokine production, T- or NK-mediated cytolysis, T cell apoptosis, cell adhesion

(continued)

TABLE 1-1

HUMAN LEUKOCYTE SURFACE ANTIGENS—THE CD CLASSIFICATION OF LEUKOCYTE DIFFERENTIATION ANTIGENS (CONTINUED)

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, KDA	DISTRIBUTION	LIGAND(S)	FUNCTION
CD3 (T3, Leu-4)	Ig	γ:25–28, δ:21–28, ε:20–25, η:21–22, ζ:16	T	Associates with the TCR	T cell activation and function; ζ is the signal transduction component of the CD3 complex
CD4 (T4, Leu-3)	Ig	55	T, myeloid	MHC-II, HIV, gp120, IL-16, SABP	T cell selection, T cell activation, signal transduction with p56lck, primary receptor for HIV
CD7 (3A1, Leu-9)	Ig	40	T, NK	K-12 (CD7L)	T and NK cell signal transduction and regulation of IFN-γ, TNF-α production
CD8 (T8, Leu-2)	Ig	34	T	MHC-I	T cell selection, T cell activation, signal transduction with p56lck
CD14 (LPS-receptor)	LRG	53–55	M, G (weak), not by myeloid progenitors	Endotoxin (lipopolysaccharide), lipoteichoic acid, PI	TLR4 mediates with LPS and other PAMP activation of innate immunity
CD16 (FcγRIIIa)	Ig	50–80	NK, macrophages, neutrophils	Fc portion of IgG	Mediates phagocytosis and ADCC
CD19 B4	Ig	95	B (except plasma cells), FDC	Not known	Associates with CD21 and CD81 to form a complex involved in signal transduction in B cell development, activation, and differentiation
CD20 (B1)	Unassigned	33–37	B (except plasma cells)	Not known	Cell signaling, may be important for B cell activation and proliferation
CD21 (B2, CR2, EBV-R, C3dR)	RCA	145	Mature B, FDC, subset of thymocytes	C3d, C3dg, iC3b, CD23, EBV	Associates with CD19 and CD81 to form a complex involved in signal transduction in B cell development, activation, and differentiation; Epstein-Barr virus receptor
CD22 (BL-CAM)	Ig	130–140	Mature B	CDw75	Cell adhesion, signaling through association with p72sky, p53/56lyn, PI3 kinase, SHP1, fLCγ
CD23 (FcεRII, B6, Leu-20, BLAST-2)	C-type lectin	45	B, M, FDC	IgE, CD21, CD11b, CD11c	Regulates IgE synthesis, cytokine release by monocytes
CD28	Ig	44	T, plasma cells	CD80, CD86	Co-stimulatory for T cell activation; involved in the decision between T cell activation and anergy
CD32 (FcγRII)	Ig	40	NK, macrophages, neutrophils	Fc portion of IgG	Mediates phagocytosis and ADCC
CD40	TNFR	48–50	B, DC, EC, thymic epithelium, MP, cancers	CD154	B cell activation, proliferation, and differentiation; formation of GCs; isotype switching; rescue from apoptosis
CD45 (LCA, T200, B220)	PTP	180, 200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	T and B activation, thymocyte development, signal transduction, apoptosis
CD45RA	PTP	210, 220	Subset T, medullary thymocytes, "naive" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 4 (A), restricted to a subset of T cells

(continued)

TABLE 1-1

HUMAN LEUKOCYTE SURFACE ANTIGENS—THE CD CLASSIFICATION OF LEUKOCYTE DIFFERENTIATION ANTIGENS (CONTINUED)

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, KDA	DISTRIBUTION	LIGAND(S)	FUNCTION
CD45RB	PTP	200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 5 (B)
CD45RC	PTP	210, 220	Subset T, medullary thymocytes, "naive" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 6 (C), restricted to a subset of T cells
CD45RO	PTP	180	Subset T, cortical thymocytes, "memory" T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing no differentially spliced exons, restricted to a subset of T cells
Surface Antigen (Other Names)	Family	Molecular Mass, kDa	Distribution	Ligand(s)	Function
CD64 (FcγRI)	Ig	45–55	Macrophages and monocytes	Fc portion of IgG	Mediates phagocytosis and ADCC
CD80 (B7-1, BB1)	Ig	60	Activated B and T, MP, DC	CD28, CD152	Co-regulator of T cell activation; signaling through CD28 stimulates and through CD152 inhibits T cell activation
CD86 (B7-2, B70)	Ig	80	Subset B, DC, EC, activated T, thymic epithelium	CD28, CD152	Co-regulator of T cell activation; signaling through CD28 stimulates and through CD152 inhibits T cell activation
CD89 (FCαR)	Ig	55–100	Neutrophils, eosinophils, monocytes, and MP	Fc portion of IgG	Mediates phagocytosis and ADCC of IgA-coated pathogens
CD95 (APO-1, Fas)	TNFR	43	Activated T and B	Fas ligand	Mediates apoptosis
CD152 (CTLA-4)	Ig	30–33	Activated T	CD80, CD86	Inhibits T cell proliferation
CD154 (CD40L)	TNF	33	Activated CD4+ T, subset CD8+ T, NK, M, basophil	CD40	Co-stimulatory for T cell activation, B cell proliferation and differentiation
CD279 (PD-1)	Ig	50–55	B, T, TfH	PD-L1, PD-L2	Inhibits T cell proliferation

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CTLA, cytotoxic T lymphocyte–associated protein; DC, dendritic cells; EBV, Epstein-Barr virus; EC, endothelial cells; ECM, extracellular matrix; Fcγ RIII, low-affinity IgG receptor isoform A; FDC, follicular dendritic cells; G, granulocytes; GC, germinal center; GPI, glycosyl phosphatidylinositol; HTA, human thymocyte antigen; Ig, immunoglobulin; IgG, immunoglobulin G; LCA, leukocyte common antigen; LPS, lipopolysaccharide; MHC-I, major histocompatibility complex class I; MP, macrophages; Mr, relative molecular mass; NK, natural killer cells; P, platelets; PBT, peripheral blood T cells; PD-1, programmed cell death-1; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PTP, protein tyrosine phosphatase; TCR, T cell receptor; TfH, T follicular helper cells; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor. For an expanded list of cluster of differentiation (CD) human antigens, see Harrison's Online at http://www.accessmedicine.com; and for a full list of CD human antigens from the most recent Human Workshop on Leukocyte Differentiation Antigens (VII), see http://mpr.nci.nih.gov/prow/.

Source: Compiled from T Kishimoto et al (eds): Leukocyte Typing VI. New York: Garland Publishing, 1997; R Brines et al: Immunology Today 18S:1, 1997; and S Shaw (ed): Protein reviews on the Web. http://mpr.nci.nih.gov/prow/.

THE INNATE IMMUNE SYSTEM

All multicellular organisms, including humans, have developed the use of a limited number of surface and intracellular germline-encoded molecules that recognize large groups of pathogens. Because of the myriad human pathogens, host molecules of the human innate immune system sense "danger signals" and either recognize PAMPs, the common molecular structures shared by many pathogens, or recognize host cell molecules produced in response to infection such as heat shock proteins and fragments of the extracellular matrix. PAMPs must be conserved structures vital to pathogen virulence and survival, such as bacterial endotoxin, so that pathogens cannot mutate molecules of PAMPs to evade human innate immune responses. PRRs are host proteins of the innate immune system that recognize PAMPs as host danger signal molecules **(Tables 1-2** and **1-3)**. Thus, recognition of pathogen molecules by hematopoietic and nonhematopoietic cell

TABLE 1-2

MAJOR COMPONENTS OF THE INNATE IMMUNE SYSTEM	
Pattern recognition receptors (PRRs)	Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid–inducible gene (RIG)-1-like receptors (RLRs), and NOD-like receptors (NLRs)
Antimicrobial peptides	α-Defensins, β-defensins, cathelin, protegrin, granulysin, histatin, secretory leukoprotease inhibitor, and probiotics
Cells	Macrophages, dendritic cells, NK cells, NK-T cells, neutrophils, eosinophils, mast cells, basophils, and epithelial cells
Complement components	Classic and alternative complement pathway, and proteins that bind complement components
Cytokines	Autocrine, paracrine, endocrine cytokines that mediate host defense and inflammation, as well as recruit, direct, and regulate adaptive immune responses

Abbreviation: NK, natural killer.

types leads to activation/production of the complement cascade, cytokines, and antimicrobial peptides as effector molecules. In addition, pathogen PAMPs as host danger signal molecules activate dendritic cells to mature and to express molecules on the dendritic cell surface that optimize antigen presentation to respond to foreign antigens.

PATTERN RECOGNITION

Major PRR families of proteins include transmembrane proteins, such as the Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and cytoplasmic proteins, such as the retinoic acid–inducible gene (RIG)-1-like receptors (RLRs) and NOD-like receptors (NLRs) (Table 1-3). A major group of PRR collagenous glycoproteins with C-type lectin domains are termed collectins and include the serum protein mannose-binding lectin (MBL). MBL and other collectins, as well as two other protein families—the pentraxins (such as C-reactive protein and serum amyloid P) and macrophage scavenger receptors—all have the property of opsonizing (coating) bacteria for phagocytosis by macrophages

TABLE 1-3

PATTERN RECOGNITION RECEPTORS (PRRS) AND THEIR LIGANDS			
PRRS	LOCALIZATION	LIGAND	ORIGIN OF THE LIGAND
TLR			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasite, self
TLR3	Endolysosome	dsRNA	Virus
TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11	Plasma membrane	Profilin-like molecule	Protozoa
RLR			
RIG-I	Cytoplasm	Short dsRNA, triphosphate dsRNA	RNA viruses, DNA virus
MDA5	Cytoplasm	Long dsRNA	RNA viruses (Picornaviridae)
LGP2	Cytoplasm	Unknown	RNA viruses
NLR			
NOD1	Cytoplasm	iE-DAP	Bacteria
NOD2	Cytoplasm	MDP	Bacteria
CLR			
Dectin-1	Plasma membrane	β^2-Glucan	Fungi
Dectin-2	Plasma membrane	β^2-Glucan	Fungi
MINCLE	Plasma membrane	SAP130	Self, fungi

Abbreviations: CLR, C-type lectin receptors; dsRNA, double-strand RNA; iE-DAP, D-glutamyl-meso-diaminopimelic acid moiety; LGP2, Laboratory of Genetics and Physiology 2 protein encoded by the gene DHX58; MDA5, melanoma differentiation-associated protein 5; MDP, MurNAc-L-Ala-D-isoGln, also known as muramyl dipeptide; MINCLE, macrophage-inducible C-type lectin; NLR, NOD-like receptor; NOD, NOTCH protein domain; RIG, retinoic acid–inducible gene; RLR, RIG-like receptors; TLR, Toll-like receptor.
Source: Adapted from O Takeuchi, S Akira: Cell 140:805, 2010, with permission.

and can also activate the complement cascade to lyse bacteria. Integrins are cell-surface adhesion molecules that affect attachment between cells and the extracellular matrix and mediate signal transduction that reflects the chemical composition of the cell environment. For example, integrins signal after cells bind bacterial lipopolysaccharide (LPS) and activate phagocytic cells to ingest pathogens.

There are multiple connections between the innate and adaptive immune systems; these include (1) a plasma protein, LPS-binding protein, that binds and transfers LPS to the macrophage LPS receptor, CD14; (2) a human family of proteins called Toll-like receptor proteins (TLRs), some of which are associated with CD14, bind LPS, and signal epithelial cells, dendritic cells, and macrophages to produce cytokines and upregulate cell-surface molecules that signal the initiation of adaptive immune responses (Fig. 1-1, Tables 1-3 and 1-4), and (3) families of intracellular microbial sensors called NLRs and RLRs. Proteins in the Toll family can be expressed on macrophages, dendritic cells, and B cells as well as on a variety of nonhematopoietic cell types, including respiratory epithelial cells. Eleven TLRs have been identified in humans, and 13 TLRs have been identified in mice (Tables 1-4 and 1-5). Upon ligation, TLRs activate a series of intracellular events that lead to the killing of bacteria- and viral-infected cells as well as to the recruitment and ultimate activation of antigen-specific T and B lymphocytes (Fig. 1-1). Importantly, signaling by massive amounts of LPS through TLR4 leads to the release of large amounts of cytokines that mediate LPS-induced shock. Mutations in TLR4 proteins in mice protect from LPS shock, and TLR mutations in humans protect from LPS-induced inflammatory diseases such as LPS-induced asthma (Fig. 1-1).

Two other families of cytoplasmic PRRs are the NLRs and the RLRs. These families, unlike the TLRs, are composed primarily of soluble intracellular proteins that scan host cell cytoplasm for intracellular pathogens (Tables 1-2 and 1-3).

The intracellular microbial sensors, NLRs, after triggering, form large cytoplasmic complexes termed in*fl*ammasomes, which are aggregates of molecules including NOD-like receptor pyrin (NLRP) proteins

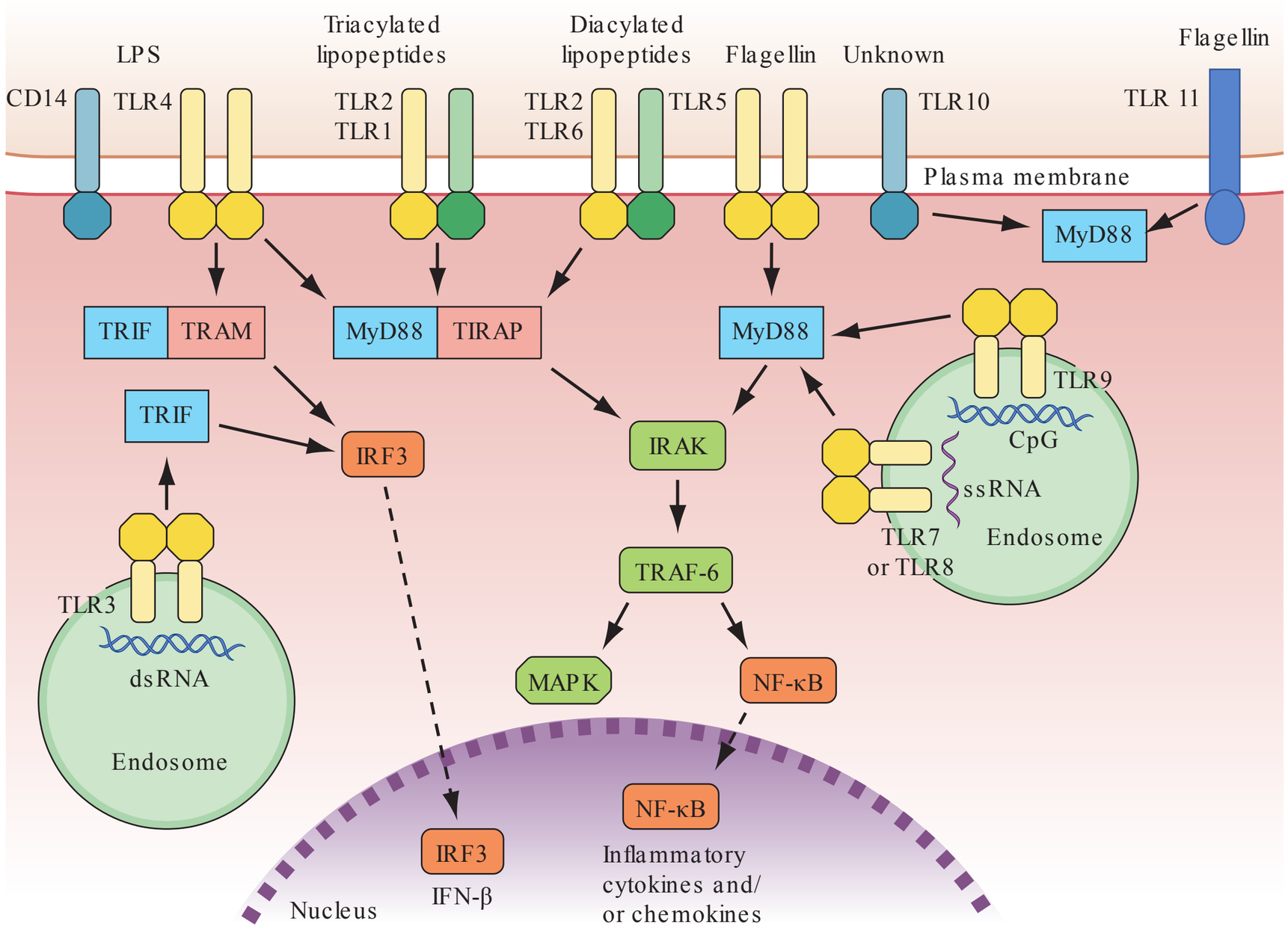


FIGURE 1-1

Overview o**f** major TLR signaling pathways. All TLRs signal through MyD88, with the exception of TLR3. TLR4 and the TLR2 subfamily (TLR1, TLR2, TLR6) also engage TIRAP. TLR3 signals through TRIF. TRIF is also used in conjunction with TRAM in the TLR4-MyD88-independent pathway. Dashed arrows indicate translocation into the nucleus. dsRNA, double-strand RNA; IFN, interferon; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; ssRNA, single-strand RNA; TLR, Toll-like receptor. (Adapted *f*rom D van Duin et al: Trends Immunol 27:49, 2006, with permission.)

TABLE 1-4

THE ROLE OF PATTERN RECOGNITION RECEPTORS (PRRS) IN MODULATION OF ADAPTIVE IMMUNE RESPONSES

PRR FAMILY	PRRS	LIGAND	DC OR MACROPHAGE CYTOKINE RESPONSE	ADAPTIVE IMMUNE RESPONSE
TLRs	TLR2 (heterodimer with TLR1 or 6)	Lipopeptides Pam-3-cys (TLR2/1) MALP (TLR2/6)	Low IL-12p70 High IL-10 IL-6	T_H1 T_H2 Tregulatory
	TLR3	dsRNA	IL-12p70 IFN-α IL-6	T_H1
	TLR4	Escherichia coli LPS	High IL-12p70 Intermediate IL-10 IL-6	T_H1
	TLR5	Flagellin	High IL-12p70 Low IL-12p70	T_H1 T_H2
	TLR7/8	ssRNA Imidazoquinolines	High IL-12p70 IFN-α IL-6	T_H1
	TLR9	CpG DNA	High IL-12p70 Low IL-10 IL-6 IFN-α	T_H1
	TLR10	?	?	?
	TLR11	Profilin-like molecule Uropathogenic bacteria	?	?
C-type lectins	DC-SIGN	Env of HIV; core protein of HCV; components of Mycobacterium tuberculosis; Helicobacter pylori, Lewis Ag	H. pylori, Lewis Ag Suppresses IL-12p70 Suppresses TLR signaling in DCs	T_H2 Tregulatory
NOD	NOD2	Muramyl dipeptide of peptidoglycan of bacteria	Induces IL-10 in DCs	Weak T cell response (tolerogenic?)
Mannose receptor	Mannose receptor	Mannosylated lipoarabinomannans from bacillus Calmette-Guérin and M. tuberculosis	Suppresses IL-12 and TLR signaling in DCs	Weak T cell response? (tolerogenic?)

Abbreviations: CpG, sequences in DNA recognized by TLR-9; DC, dendritic cell; DC-SIGN, DC-specifc C-type lectin; dsRNA, double-strand RNA; HCV, hepatitis C; HIV, human immunodefciency virus; LPS, lipopolysaccharide; MALP, macrophage-activating lipopeptide; NOD, NOTCH protein domain; ssRNA, single-strand RNA; T_H1, helper T cell; T_H2, helper T cell; TLR, Toll-like receptor.

Source: B Pulendran: J Immunol 174:2457, 2005. Copyright 2005 The American Association of Immunologists, Inc., with permission.

that are members of the NLR family (Table 1-3). Inflammasomes activate inflammatory caspases and IL-1β in the presence of nonbacterial danger signals (cell stress) and bacterial PAMPs. Mutations in inflammasome proteins can lead to chronic inflammation in a group of periodic febrile diseases called autoin*fl*ammatory syndromes (Table 1-6).

EFFECTOR CELLS OF INNATE IMMUNITY

Cells of the innate immune system and their roles in the first line of host defense are listed in Table 1-5. Equally important as their roles in the mediation of innate immune responses are the roles that each cell type plays in recruiting T and B lymphocytes of the adaptive immune system to engage in specific pathogen responses.

Monocytes-macrophages

Monocytes arise from precursor cells within bone marrow **(Fig. 1-2)** and circulate with a half-life ranging from 1 to 3 days. Monocytes leave the peripheral circulation via capillaries and migration into a vast extravascular cellular pool. Tissue macrophages arise from monocytes that have migrated out of the circulation and by in situ proliferation of macrophage precursors in tissue. Common locations where tissue macrophages (and certain of their specialized forms) are found are lymph node, spleen, bone marrow, perivascular connective tissue, serous cavities such as the peritoneum, pleura, skin connective tissue, lung (alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), central nervous system (microglia cells), and synovium (type A lining cells).

TABLE 1-5

CELLS OF THE INNATE IMMUNE SYSTEM AND THEIR MAJOR ROLES IN TRIGGERING ADAPTIVE IMMUNITY

CELL TYPE	MAJOR ROLE IN INNATE IMMUNITY	MAJOR ROLE IN ADAPTIVE IMMUNITY
Macrophages	Phagocytose and kill bacteria; produce antimicrobial peptides; bind LPS; produce inflammatory cytokines	Produce IL-1 and TNF-α to upregulate lymphocyte adhesion molecules and chemokines to attract antigen-specific lymphocyte. Produce IL-12 to recruit T_H1 T helper cell responses; upregulate co-stimulatory and MHC molecules to facilitate T and B lymphocyte recognition and activation. Macrophages and dendritic cells, after LPS signaling, upregulate co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) that are required for activation of pathogen-specific T cells. There are also Toll-like proteins on B cells and dendritic cells that, after LPS ligation, induce CD80 and CD86 on these cells for T cell antigen presentation.
Plasmacytoid dendritic cells (DCs) of lymphoid lineage	Produce large amounts of interferon-α (IFN-α), which has antitumor and antiviral activity, and are found in T cell zones of lymphoid organs; they circulate in blood	IFN-α is a potent activator of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells
Myeloid dendritic cells are of two types: interstitial and Langerhans-derived	Interstitial DCs are strong producers of IL-12 and IL-10 and are located in T cell zones of lymphoid organs, circulate in blood, and are present in the interstices of the lung, heart, and kidney; Langerhans DCs are strong producers of IL-12; are located in T cell zones of lymph nodes, skin epithelia, and the thymic medulla; and circulate in blood	Interstitial DCs are potent activators of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells
Natural killer (NK) cells	Kill foreign and host cells that have low levels of MHC+ self-peptides. Express NK receptors that inhibit NK function in the presence of high expression of self-MHC.	Produce TNF-α and IFN-γ, which recruit T_H1 helper T cell responses
NK-T cells	Lymphocytes with both T cell and NK surface markers that recognize lipid antigens of intracellular bacteria such as Mycobacterium tuberculosis by CD1 molecules and kill host cells infected with intracellular bacteria.	Produce IL-4 to recruit T_H2 helper T cell responses, IgG1 and IgE production
Neutrophils	Phagocytose and kill bacteria, produce antimicrobial peptides	Produce nitric oxide synthase and nitric oxide, which inhibit apoptosis in lymphocytes and can prolong adaptive immune responses
Eosinophils	Kill invading parasites	Produce IL-5, which recruits Ig-specific antibody responses
Mast cells and basophils	Release TNF-α, IL-6, and IFN-γ in response to a variety of bacterial PAMPs	Produce IL-4, which recruits T_H2 helper T cell responses, and recruit IgG1- and IgE-specific antibody responses
Epithelial cells	Produce antimicrobial peptides; tissue-specific epithelia produce mediator of local innate immunity; e.g., lung epithelial cells produce surfactant proteins (proteins within the collectin family) that bind and promote clearance of lung-invading microbes	Produces TGF-β, which triggers IgA-specific antibody responses

Abbreviations: IL-4, IL-5, IL-6, IL-10, and IL-12, interleukin 4, 5, 6, 10, and 12, respectively; MHC, major histocompatibility complex: LPS, lipopolysaccharide; PAMP, pathogen-associated molecular patterns; T_H, helper T cell; TNF-α, tumor necrosis factor-alpha.

Source: Adapted from R Medzhitov, CA Janeway: Curr Opinion Immunol 9:4, 1997. Copyright 1997, with permission from Elsevier.

TABLE 1-6

DISEASES ASSOCIATED WITH INFLAMMASOME ACTIVITY

DISEASE	CLINICAL FEATURES	GENE MUTATED	ETIOLOGIC AGENT	INFLAMMASOME INVOLVEMENT	ANAKINRA RESPONSE[a]
Familial cold autoinflammatory syndrome (FCAS)	Fever, arthralgia, cold-induced urticaria	NALP3		Overactive	Yes
Muckle-Wells syndrome (MWS)	Fever, arthralgia, urticaria, sensorineural deafness, amyloidosis	NALP3		Overactive	Yes
Chronic infantile neurologic cutaneous and articular syndrome (CINCA, NOMID)	Fever, severe arthralgia, urticaria, neurologic problems, severe amyloidosis	NALP3		Overactive	Yes
Familial Mediterranean fever (FMF)	Fever, peritonitis, pleuritis, amyloidosis	Pyrin		Overactive	Partial
Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA)	Pyogenic sterile arthritis	PSTPIP1		Overactive	Yes
Hyperimmunoglobulin D syndrome (HIDS)	Arthralgia, abdominal pain, lymphadenopathy	Mevalonate kinase		To be demonstrated	Yes
Tumor necrosis factor receptor-1–associated syndrome (TRAPS)	Fever, abdominal pain, skin lesions	TNF-R1		To be demonstrated	Yes
Systemic-onset juvenile idiopathic arthritis (SOJIA)	Chronic joint inflammation		Unknown	To be demonstrated	Yes
Adult-onset Still's disease (AOSD)	Arthralgia, fever		Unknown	To be demonstrated	Yes
Behçet's disease	Arthralgia, uveitis, ulcers		Unknown	To be demonstrated	Yes
Schnitzler's syndrome	Urticaria, fever, arthralgia		Unknown	To be demonstrated	Yes
Gout	Metabolic arthritis, pain		Uric acid (MSU)	Activated	Yes
Pseudogout	Arthritis		CPPD	Activated	Yes
Contact dermatitis	Urticaria		Irritants	Activated	Unknown
Fever syndrome	Fever	NALP12		Unknown	Unknown
Hydatidiform mole	Hydatid mole	NALP7		Unknown	Unknown
Vitiligo	Skin depigmentation, autoimmunity	NLRP1		Overactive	Unknown
Crohn's disease		NLRP3		Underactive	Unknown
Multiple Sclerosis		NLPR3		Activated	Unknown
Psoriasitic arthritis		NLRP3		Activated	Yes

[a]Anakinra is a recombinant interleukin-1 (IL-1) receptor antagonist that functions to block the biologic activity of naturally occurring IL-1.
Abbreviation: CPPD, calcium pyrophosphate dehydrate.
Source: Adapted from F Martinon et al: Ann Rev Immunol 27:229, 2009. Copyright 2009. Reproduced with permission from Annual Reviews Inc.

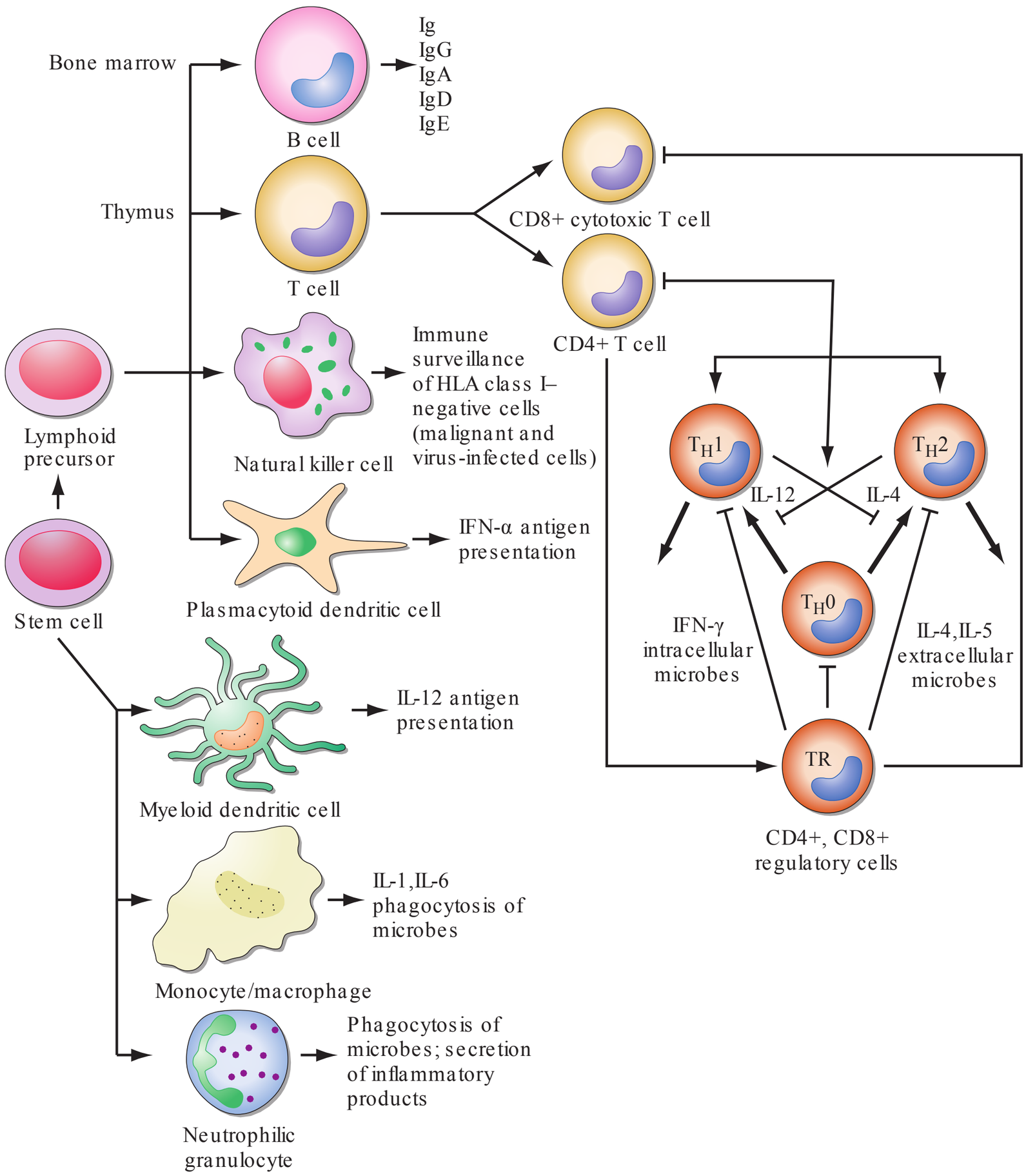


FIGURE 1-2

Schematic model of intercellular interactions of adaptive immune system cells. In this figure, the arrows denote that cells develop from precursor cells or produce cytokines or antibodies; lines ending with bars indicate suppressive intercellular interactions. Stem cells differentiate into either T cells, antigen-presenting dendritic cells, natural killer cells, macrophages, granulocytes, or B cells. Foreign antigen is processed by dendritic cells, and peptide fragments of foreign antigen are presented to CD4+ and/or CD8+ T cells. CD8+ T cell activation leads to induction of cytotoxic T lymphocyte (CTL) or killer T cell generation, as well as induction of cytokine-producing CD8+ cytotoxic T cells. For antibody production against the same antigen, active antigen is bound to sIg within the B cell receptor complex and drives B cell maturation into plasma cells that secrete Ig. T_H1 or T_H2 CD4+ T cells producing interleukin (IL) 4, IL-5, or interferon (IFN) γ regulate the Ig class switching and determine the type of antibody produced. T_H17 cells secrete IL-17, IL-22, IL-26, which contribute to host defense against extracellular bacteria and fungi, particularly at mucosal surfaces. CD4+, CD25+ T regulatory cells produce IL-10 and downregulate T and B cell responses once the microbe has been eliminated. GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF, tumor necrosis factor.

In general, monocytes-macrophages are on the first line of defense associated with innate immunity and ingest and destroy microorganisms through the release of toxic products such as hydrogen peroxide (H_2O_2) and nitric oxide (NO). Inflammatory mediators produced by macrophages attract additional effector cells such as neutrophils to the site of infection. Macrophage mediators include prostaglandins; leukotrienes; platelet activating factor; cytokines such as IL-1, TNF-α, IL-6, and IL-12; and chemokines **(Tables 1-7** to **1-9)**.

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-1α, β	Type I IL-1r, Type II IL-1r	Monocytes/macrophages, B cells, fibroblasts, most epithelial cells including thymic epithelium, endothelial cells	All cells	Upregulates adhesion molecule expression, neutrophil and macrophage emigration, mimics shock, fever, upregulates hepatic acute-phase protein production, facilitates hematopoiesis
IL-2	IL-2r α, β, common γ	T cells	T cells, B cells, NK cells, monocytes-macrophages	Promotes T cell activation and proliferation, B cell growth, NK cell proliferation and activation, enhanced monocyte/macrophage cytolytic activity
IL-3	IL-3r, common β	T cells, NK cells, mast cells	Monocytes-macrophages, mast cells, eosinophils, bone marrow progenitors	Stimulates hematopoietic progenitors
IL-4	IL-4r α, common γ	T cells, mast cells, basophils	T cells, B cells, NK cells, monocytes-macrophages, neutrophils, eosinophils, endothelial cells, fibroblasts	Stimulates T_H2 helper T cell differentiation and proliferation; stimulates B cell Ig class switch to IgG1 and IgE anti-inflammatory action on T cells, monocytes; produced by T follicular helper cells in B cell germinal centers that stimulate B cell maturation
IL-5	IL-5r α, common γ	T cells, mast cells, eosinophils	Eosinophils, basophils, murine B cells	Regulates eosinophil migration and activation
IL-6	IL-6r, gp130	Monocytes-macrophages, B cells, fibroblasts, most epithelium including thymic epithelium, endothelial cells	T cells, B cells, epithelial cells, hepatocytes, monocytes-macrophages	Induces acute-phase protein production, T and B cell differentiation and growth, myeloma cell growth, and osteoclast growth and activation
IL-7	IL-7r α, common γ	Bone marrow, thymic epithelial cells	T cells, B cells, bone marrow cells	Differentiates B, T, and NK cell precursors, activates T and NK cells
IL-8	CXCR1, CXCR2	Monocytes-macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells	Neutrophils, T cells, monocytes-macrophages, endothelial cells, basophils	Induces neutrophil, monocyte, and T cell migration, induces neutrophil adherence to endothelial cells and histamine release from basophils, and stimulates angiogenesis; suppresses proliferation of hepatic precursors
IL-9	IL-9r α, common γ	T cells	Bone marrow progenitors, B cells, T cells, mast cells	Induces mast cell proliferation and function, synergizes with IL-4 in IgG and IgE production and T cell growth, activation, and differentiation
IL-10	IL-10r	Monocytes-macrophages, T cells, B cells, keratinocytes, mast cells	Monocytes-macrophages, T cells, B cells, NK cells, mast cells	Inhibits macrophage proinflammatory cytokine production, downregulates cytokine class II antigen and B7-1 and B7-2 expression, inhibits differentiation of T_H1 helper T cells, inhibits NK cell function, stimulates mast cell proliferation and function, B cell activation, and differentiation
IL-11	IL-11r α, gp130	Bone marrow stromal cells	Megakaryocytes, B cells, hepatocytes	Induces megakaryocyte colony formation and maturation, enhances antibody responses, stimulates acute-phase protein production

(continued)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (CONTINUED)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-12 (35-kDa and 40-kDa subunits)	IL-12r	Activated macrophages, dendritic cells, neutrophils	T cells, NK cells	Induces T_H1 T helper cell formation and lymphokine-activated killer cell formation; increases CD8+ CTL cytolytic activity; ↓ IL-17, ↑ IFN-γ
IL-13	IL-13r/IL-4r α	T cells (T_H2)	Monocytes-macrophages, B cells, endothelial cells, keratinocytes	Upregulates VCAM-1 and C-C chemokine expression on endothelial cells and B cell activation and differentiation, and inhibits macrophage proinflammatory cytokine production
IL-14	Unknown	T cells	Normal and malignant B cells	Induces B cell proliferation, inhibits antibody secretion, and expands selected B cell subgroups
IL-15	IL-15r α, common γ, IL2r β	Monocytes-macrophages, epithelial cells, fibroblasts	T cells, NK cells	Promotes T cell activation and proliferation, angiogenesis, and NK cells
IL-16	CD4	Mast cells, eosinophils, CD8+ T cells, respiratory epithelium	CD4+ T cells, monocytes-macrophages, eosinophils	Promotes chemoattraction of CD4+ T cells, monocytes, and eosinophils; inhibits HIV replication; inhibits T cell activation through CD3/T cell receptor
IL-17	IL-17r	CD4+ T cells	Fibroblasts, endothelium, epithelium, macrophages	Enhances cytokine/chemokine secretion; promotes delayed-type reactions
IL-18	IL-18r (IL-1R-related protein)	Keratinocytes, macrophages	T cells, B cells, NK cells	Upregulates IFN-γ production, enhances NK cell cytotoxicity
IL-21	IL-δγ chain/ IL-21R	CD4 T cells	NK cells	Downregulates NK cell–activating molecules, NKG2D/DAP10; produced by T follicular helper cells in B cell germinal centers that stimulate B cell maturation.
IL-22	IL-22 R1/IL-10R2	DC, T cells	Epithelial cells	Innate responses against bacterial pathogens; promotes hepatocyte survival
IL-23	IL-12Rb1/IL23R	Macrophages, other cell types	T cells	Opposite effects of IL-12 (↑ IL-17, ↑ IFN-γ)
IL-24	IL-20 R1/IL-20R2 IL-22R1/IL-20 R2	Macrophages, T_H2 cells	Nonhematopoietic cells such as fibroblasts	Promotes wound healing
IL-25 (also called IL-17E)	IL-17RB	CD4 T cells, mast cells	Fibroblasts, endothelium, epithelium, macrophages	Proinflammatory; induces cytokine production
IL-26	IL-20 R1/IL-10R2	T_H1, T_H17 T cells, synovial cells	Epithelial cells	Proinflammatory; induces cytokine production
IFN-α	Type I interferon receptor	All cells	All cells	Promotes antiviral activity; stimulates T cell, macrophage, and NK cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions
IFN-β	Type I interferon receptor	All cells	All cells	Antiviral activity; stimulates T cell, macrophage, and NK cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions
IFN-γ	Type II interferon receptor	T cells, NK cells	All cells	Regulates macrophage and NK cell activations; stimulates immunoglobulin secretion by B cells; induction of class II histocompatibility antigens; T_H1 T cell differentiation

(continued)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (CONTINUED)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
TNF-α	TNFrI, TNFrII	Monocytes-macrophages, mast cells, basophils, eosinophils, NK cells, B cells, T cells, keratinocytes, fibroblasts, thymic epithelial cells	All cells except erythrocytes	Fever, anorexia, shock, capillary leak syndrome, enhanced leukocyte cytotoxicity, enhanced NK cell function, acute phase protein synthesis, proinflammatory cytokine induction
TNF-β	TNFrI, TNFrII	T cells, B cells	All cells except erythrocytes	Cell cytotoxicity, lymph node and spleen development
LT-β	LTβR	T cells	All cells except erythrocytes	Cell cytotoxicity, normal lymph node development
G-CSF	G-CSFr; gp130	Monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells, stromal cells	Myeloid cells, endothelial cells	Regulates myelopoiesis; enhances survival and function of neutrophils; clinical use in reversing neutropenia after cytotoxic chemotherapy
GM-CSF	GM-CSFr, common β	T cells, monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells	Monocytes-macrophages, neutrophils, eosinophils, fibroblasts, endothelial cells	Regulates myelopoiesis; enhances macrophage bactericidal and tumoricidal activity; mediator of dendritic cell maturation and function; upregulates NK cell function; clinical use in reversing neutropenia after cytotoxic chemotherapy
M-CSF	M-CSFr (c-*f*ms protooncogene)	Fibroblasts, endothelial cells, monocytes-macrophages, T cells, B cells, epithelial cells including thymic epithelium	Monocytes-macrophages	Regulates monocyte-macrophage production and function
LIF	LIFr-α; gp130	Activated T cells, bone marrow stromal cells, thymic epithelium	Megakaryocytes, monocytes, hepatocytes, possibly lymphocyte subpopulations	Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis
OSM	OSMr; LIFr; gp130	Activated monocytes-macrophages and T cells, bone marrow stromal cells, some breast carcinoma cell lines, myeloma cells	Neurons, hepatocytes, monocytes-macrophages, adipocytes, alveolar epithelial cells, embryonic stem cells, melanocytes, endothelial cells, fibroblasts, myeloma cells	Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis; stimulates growth of Kaposi's sarcoma cells
SCF	SCFr (c-kit protooncogene)	Bone marrow stromal cells and fibroblasts	Embryonic stem cells, myeloid and lymphoid precursors, mast cells	Stimulates hematopoietic progenitor cell growth, mast cell growth; promotes embryonic stem cell migration
TGF-β (3 isoforms)	Type I, II, III TGF-β receptor	Most cell types	Most cell types	Downregulates T cell, macrophage, and granulocyte responses; stimulates synthesis of matrix proteins; stimulates angiogenesis
Lymphotactin/ SCM-1	XCR1	NK cells, mast cells, double-negative thymocytes, activated CD8+ T cells	T cells, NK cells	Chemoattractant for lymphocytes; only known chemokine of C class

(continued)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (CONTINUED)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
MCP-1	CCR2	Fibroblasts, smooth-muscle cells, activated PBMCs	Monocytes-macrophages, NKcells, memory Tcells, basophils	Chemoattractant for monocytes, activated memory Tcells, and NKcells; induces granule release from CD8+ Tcells and NKcells; potent histamine-releasing factor for basophils; suppresses proliferation of hematopoietic precursors; regulates monocyte protease production
MCP-2	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, Tcells, eosinophils, basophils, NKcells	Chemoattractant for monocytes, memory and naïve Tcells, eosinophils, ?NKcells; activates basophils and eosinophils; regulates monocyte protease production
MCP-3	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, Tcells, eosinophils, basophils, NK cells, dendritic cells	Chemoattractant for monocytes, memory and naïve Tcells, dendritic cells, eosinophils, ?NKcells; activates basophils and eosinophils; regulates monocyte protease production
MCP-4	CCR2, CCR3	Lung, colon, small intestinal epithelial cells, activated endothelial cells	Monocytes-macrophages, Tcells, eosinophils, basophils	Chemoattractant for monocytes, Tcells, eosinophils, and basophils
Eotaxin	CCR3	Pulmonary epithelial cells, heart	Eosinophils, basophils	Potent chemoattractant for eosinophils and basophils; induces allergic airways disease; acts in concert with IL-5 to activate eosinophils; antibodies to eotaxin inhibit airway inflammation
TARC	CCR4	Thymus, dendritic cells, activated T cells	Tcells, NKcells	Chemoattractant for Tand NKcells
MDC	CCR4	Monocytes-macrophages, dendritic cells, thymus	Activated Tcells	Chemoattractant for activated Tcells; inhibits infection with Tcell tropic HIV
MIP-1α	CCR1, CCR5	Monocytes-macrophages, Tcells	Monocytes-macrophages, Tcells, dendritic cells, NKcells, eosinophils, basophils	Chemoattractant for monocytes, Tcells, dendritic cells, and NKcells, and weak chemoattractant for eosinophils and basophils; activates NKcell function; suppresses proliferation of hematopoietic precursors; necessary for myocarditis associated with coxsackievirus infection; inhibits infection with monocytotropic HIV
MIP-1β	CCR5	Monocytes-macrophages, Tcells	Monocytes-macrophages, Tcells, NKcells, dendritic cells	Chemoattractant for monocytes, Tcells, and NK cells; activates NKcell function; inhibits infection with monocytotropic HIV
RANTES	CCR1, CCR2, CCR5	Monocytes-macrophages, Tcells, fbroblasts, eosinophils	Monocytes-macrophages, Tcells, NKcells, dendritic cells, eosinophils, basophils	Chemoattractant for monocytes-macrophages, CD4+, CD45Ro+ Tcells, CD8+ Tcells, NKcells, eosinophils, and basophils; induces histamine release from basophils; inhibits infections with monocytotropic HIV
LARC/ MIP-3α/ Exodus-1	CCR6	Dendritic cells, fetal liver cells, activated Tcells	Tcells, Bcells	Chemoattractant for lymphocytes
ELC/ MIP-3β	CCR7	Thymus, lymph node, appendix	Activated Tcells and Bcells	Chemoattractant for Band Tcells; receptor upregulated on EBV-infected Bcells and HSV-infected Tcells
I-309/ TCA-3	CCR8	Activated Tcells	Monocytes-macrophages, Tcells	Chemoattractant for monocytes; prevents glucocorticoid-induced apoptosis in some Tcell lines

(continued)

TABLE 1-7

CYTOKINES AND CYTOKINE RECEPTORS (CONTINUED)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
SLC/ TCA-4/ Exodus-2	CCR7	Thymic epithelial cells, lymph node, appendix, and spleen	T cells	Chemoattractant for T lymphocytes; inhibits hematopoiesis
DC-CK1/ PARC	Unknown	Dendritic cells in secondary lymphoid tissues	Naïve T cells	May have a role in induction of immune responses
TECK	CCR9	Dendritic cells, thymus, liver, small intestine	T cells, monocytes-macrophages, dendritic cells	Thymic dendritic cell-derived cytokine, possibly involved in T cell development
GRO-α/ MGSA	CXCR2	Activated granulocytes, monocyte-macrophages, and epithelial cells	Neutrophils, epithelial cells, ?endothelial cells	Neutrophil chemoattractant and activator; mitogenic for some melanoma cell lines; suppresses proliferation of hematopoietic precursors; angiogenic activity
GRO-β/ MIP-2α	CXCR2	Activated granulocytes and monocyte-macrophages	Neutrophils and ?endothelial cells	Neutrophil chemoattractant and activator; angiogenic activity
NAP-2	CXCR2	Platelets	Neutrophils, basophils	Derived from platelet basic protein; neutrophil chemoattractant and activator
IP-10	CXCR3	Monocytes-macrophages, T cells, fibroblasts, endothelial cells, epithelial cells	Activated T cells, tumor-infiltrating lymphocytes, ?endothelial cells, ?NK cells	IFN-γ-inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors
MIG	CXCR3	Monocytes-macrophages, T cells, fibroblasts	Activated T cells, tumor-infiltrating lymphocytes	IFN-γ-inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors
SDF-1	CXCR4	Fibroblasts	T cells, dendritic cells, ?basophils, ?endothelial cells	Low-potency, high-efficacy T cell chemoattractant; required for B-lymphocyte development; prevents infection of CD4+, CXCR4+ cells by T cell tropic HIV
Fractalkine	CX3CR1	Activated endothelial cells	NK cells, T cells, monocytes-macrophages	Cell-surface chemokine/mucin hybrid molecule that functions as a chemoattractant, leukocyte activator, and cell adhesion molecule
PF-4	Unknown	Platelets, megakaryocytes	Fibroblasts, endothelial cells	Chemoattractant for fibroblasts; suppresses proliferation of hematopoietic precursors; inhibits endothelial cell proliferation and angiogenesis

Abbreviations: B7-1, CD80; B7-2, CD86; CCR, CC-type chemokine receptor; CXCR, CXC-type chemokine receptor; DC-CK, dendritic cell chemokine; EBV, Epstein-Barr virus; ELC, EB11 ligand chemokine (MIP-1b); G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRP, growth-related peptide; HSV, herpes simplex virus; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IP-10, IFN-γ-inducible protein-10; LARC, liver- and activation-regulated chemokine; LIF, leukemia inhibitory factor; MCP, monocyte chemotactic protein; M-CSF, macrophage colony-stimulating factor; MDC, macrophage-derived chemokine; MGSA, melanoma growth-stimulating activity; MHC, major histocompatibility complex; MIG, monokine induced by IFN-γ; MIP, macrophage inflammatory protein; NAP, neutrophil-activating protein; NK, natural killer; OSM, oncostatin M; PARC, pulmonary- and activation-regulated chemokine; PBMC, peripheral blood mononuclear cells; PF, platelet factor; RANTES, regulated on activation, normally T cell–expressed and –secreted; SCF, stem cell factor; SDF, stromal cell–derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus- and activation-regulated chemokine; TCA, T cell activation protein; TECK, thymus expressed chemokine; TGF, transforming growth factor; T_H1 and T_H2, helper T cell subsets; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Source: Data from JS Sundy et al: Appendix B, in Inflammation, Basic Principles and Clinical Correlates, 3rd ed, J Gallin and R Snyderman (eds). Philadelphia, Lippincott Williams and Wilkins, 1999.

TABLE 1-8

CC, CXC_1, CX_3, C_1, AND XC FAMILIES OF CHEMOKINES AND CHEMOKINE RECEPTORS

CHEMOKINE RECEPTOR	CHEMOKINE LIGANDS	CELL TYPES	DISEASE CONNECTION
CCR1	CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL14 (HCC1)	T cells, monocytes, eosinophils, basophils	Rheumatoid arthritis, multiple sclerosis
CCR2	CCL2 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4), CCL16 (HCC4)	Monocytes, dendritic cells (immature), memory T cells	Atherosclerosis, rheumatoid arthritis, multiple sclerosis, resistance to intracellular pathogens, type 2 diabetes mellitus
CCR3	CCL11 (eotaxin), CCL13 (eotaxin-2), CCL7 (MCP-3), CCL5 (RANTES), CCL8 (MCP-2), CCL13 (MCP-4)	Eosinophils, basophils, mast cells, T_H2, platelets	Allergic asthma and rhinitis
CCR4	CCL17 (TARC), CCL22 (MDC)	T cells (T_H2), dendritic cells (mature), basophils, macrophages, platelets	Parasitic infection, graft rejection, T cell homing to skin
CCR5	CCL3 (MIP-1α), CCL4 (MIP-1α), CCL5 (RANTES), CCL11 (eotaxin), CCL14 (HCC1), CCL16 (HCC4)	T cells, monocytes	HIV-1 co-receptor (T cell–tropic strains), transplant rejection
CCR6	CCL20 (MIP-3α, LARC)	T cells (T regulatory and memory), B cells, dendritic cells	Mucosal humoral immunity, allergic asthma, intestinal T cell homing
CCR7	CCL19 (ELC), CCL21 (SLC)	T cells, dendritic cells (mature)	Transport of T cells and dendritic cells to lymph nodes, antigen presentation, and cellular immunity
CCR8	CCL1 (1309)	T cells (T_H2), monocytes, dendritic cells	Dendritic cell migration to lymph node, type 2 cellular immunity, granuloma formation
CCR9	CCL25 (TECK)	T cells, IgA+ plasma cells	Homing of T cells and IgA+ plasma cells to the intestine, inflammatory bowel disease
CCR10	CCL27 (CTACK), CCL28 (MEC)	T cells	T cell homing to intestine and skin
CXCR1	CXCL8 (interleukin-8), CXCL6 (GCP2)	Neutrophils, monocytes	Inflammatory lung disease, COPD
CXCR2	CXCL8, CXCL1 (GROα), CXCL2 (GROα), CXCL3 (GROα), CXCL5 (ENA-78), CXCL6	Neutrophils, monocytes, microvascular endothelial cells	Inflammatory lung disease, COPD, angiogenic for tumor growth
CXCR3-A	CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Type 1 helper cells, mast cells, mesangial cells	Inflammatory skin disease, multiple sclerosis, transplant rejection
CXCR3-B	CXCL4 (PF4), CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Microvascular endothelial cells, neoplastic cells	Angiostatic for tumor growth
CXCR4	CXCL12 (SDF-1)	Widely expressed	HIV-1 co-receptor (T cell–tropic), tumor metastases, hematopoiesis
CXCR5	CXCL13 (BCA-1)	B cells, follicular helper T cells	Formation of B cell follicles
CXCR6	CXCL16 (SR-PSOX)	CD8+ T cells, natural killer cells, and memory CD4+ T cells	Inflammatory liver disease, atherosclerosis (CXCL16)
CX_3CR1	CX3CL1 (fractalkine)	Macrophages, endothelial cells, smooth-muscle cells	Atherosclerosis
XCR1	XCL1 (lymphotactin), XCL2	T cells, natural killer cells	Rheumatoid arthritis, IgA nephropathy, tumor response

Abbreviations: BCA-1, B-cell chemoattractant 1; COPD, chronic obstructive pulmonary disease; CTACK, cutaneous T cell–attracting chemokine; ELC, Epstein-Barr I1-ligand chemokine; ENA, epithelial cell–derived neutrophil-activating peptide; GCP, granulocyte chemotactic protein; GRO, growth-regulated oncogene; HCC, hemofiltrate chemokine; IP-10, interferon inducible 10; I-TAC, interferon-inducible T cell alpha chemoattractant; LARC, liver- and activation-regulated chemokine; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mammary-enriched chemokine; MIG, monokine induced by interferon-γ; MIP, macrophage inflammatory protein; PF, platelet factor; SDF, stromal cell–derived factor; SLC, secondary lymphoid-tissue chemokine; SR-PSOX, scavenger receptor for phosphatidylserine-containing oxidized lipids; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine; T_H2, type 2 helper T cells.

Source: From IF Charo, RM Ranshohoff: N Engl J Med 354:610, 2006, with permission. Copyright Massachusetts Medical Society. All rights reserved.

TABLE 1-9

CYTOKINE FAMILIES GROUPED BY STRUCTURAL SIMILARITY	
Hematopoietins	IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, IL-16, IL-17, IL-21, IL-23, EPO, LIF, GM-CSF, G-CSF, OSM, CNTF, GH, and TPO TNF-α, LT-α, LT-β, CD40L, CD30L, CD27L, 4-1BBL, OX40, OPG, and FasL
IL-1	IL-1α, IL-1β, IL-1ra, IL-18, bFGF, aFGF, and ECGF
PDGF	PDGF A, PDGF B, and M-CSF
TGF-β	TGF-β and BMPs (1, 2, 4, etc.)
C-X-C chemokines	IL-8, Gro-α/β/γ, NAP-2, ENA78, GCP-2, PF4, CTAP-3, MIG, and IP-10
C-C chemokines	MCP-1, MCP-2, MCP-3, MIP-1α, MIP-1β, RANTES

Abbreviations: aFGF, acidic fbroblast growth factor; 4-1BBL, 401 BB ligand; bFGF, basic fbroblast growth factor; BMP, bone marrow morphogenetic proteins; C-C, cysteine-cysteine; CD, cluster of differentiation; CNTF, ciliary neurotrophic factor; CTAP, connective tissue–activating peptide; C-X-C, cysteine-x-cysteine; ECGF, endothelial cell growth factor; EPO, erythropoietin; FasL, Fas ligand; GCP-2, granulocyte chemotactic protein 2; G-CSF, granulocyte colony-stimulating factor; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; Gro, growth-related gene products; IFN, interferon; IL, interleukin; IP, interferon-γ inducible protein; LIF, leukemia inhibitory factor; LT, lymphotoxin; MCP, monocyte chemoattractant; M-CSF, macrophage colony-stimulating factor; MIG, monokine induced by interferon-γ; MIP, macrophage inflammatory protein; NAP-2, neutrophil activating protein 2; OPG, osteoprotegerin; OSM, oncostatin M; PDGF, platelet-derived growth factor; PF, platelet factor; R, receptor; RANTES, regulated on activation, normal T cell–expressed and –secreted; TGF, transforming growth factor; TNF, tumor necrosis factor; TPO, thyroperoxidase.

Although monocytes-macrophages were originally thought to be the major antigen-presenting cells (APCs) of the immune system, it is now clear that cell types called dendritic cells are the most potent and effective APCs in the body (see below). Monocytes-macrophages mediate innate immune effector functions such as destruction of antibody-coated bacteria, tumor cells, or even normal hematopoietic cells in certain types of autoimmune cytopenias. Monocytes-macrophages ingest bacteria or are infected by viruses, and in doing so, they frequently undergo programmed cell death or apoptosis. Macrophages that are infected by intracellular infectious agents are recognized by dendritic cells as infected and apoptotic cells and are phagocytosed by dendritic cells. In this manner, dendritic cells "cross-present" infectious agent antigens of macrophages to T cells. Activated macrophages can also mediate antigen-nonspecific lytic activity and eliminate cell types such as tumor cells in the absence of antibody. This activity is largely mediated by cytokines (i.e., TNF-α and IL-1). Monocytes-macrophages express lineage-specific molecules (e.g., the cell-surface LPS receptor, CD14) as well as surface receptors for a number of molecules, including the Fc region of IgG, activated complement components, and various cytokines (Table 1-7).

Dendritic cells

Human dendritic cells (DCs) contain several subsets, including myeloid DCs and plasmacytoid DCs. Myeloid DCs can differentiate into either macrophages-monocytes or tissue-specific DCs. In contrast to myeloid DCs, plasmacytoid DCs are inefficient APCs but are potent producers of type I interferon (IFN) (e.g., IFN-α) in response to viral infections. The maturation of DCs is regulated through cell-to-cell contact and soluble factors, and DCs attract immune effectors through secretion of chemokines. When DCs come in contact with bacterial products, viral proteins, or host proteins released as danger signals from distressed host cells (Figs. 1-2 and 1-3), infectious agent molecules bind to various TLRs and activate DCs to release cytokines and chemokines that drive cells of the innate immune system to become activated to respond to the invading organism, and recruit T and B cells of the adaptive immune system to respond. Plasmacytoid DCs produce antiviral IFN-α that activates NK cell killing of pathogen-infected cells; IFN-α also activates T cells to mature into antipathogen cytotoxic (killer) T cells. Following contact with pathogens, both plasmacytoid and myeloid DCs produce chemokines that attract helper and cytotoxic T cells, B cells, polymorphonuclear cells, and naïve and memory T cells as well as regulatory T cells to ultimately dampen the immune response once the pathogen is controlled. TLR engagement on DCs upregulates MHC class II, B7-1 (CD80), and B7-2 (CD86), which enhance DC-specific antigen presentation and induce cytokine production (Table 1-7). Thus, DCs are important bridges between early (innate) and later (adaptive) immunity. DCs also modulate and determine the types of immune responses induced by pathogens via the TLRs expressed on DCs (TLR7–9 on plasmacytoid DCs, TLR4 on monocytoid DCs) and via the TLR adapter proteins that are induced to associate with TLRs (Fig. 1-1, Table 1-4). In addition, other PRRs, such as C-type lectins, NLRs, and mannose receptors, upon ligation by pathogen products, activate cells of the adaptive immune system and, like TLR stimulation, by a variety of factors, determine the type and quality of the adaptive immune response that is triggered (Table 1-4).

Large granular lymphocytes/natural killer cells

Large granular lymphocytes (LGLs) or NK cells account for ~5–15% of peripheral blood lymphocytes. NK cells are nonadherent, nonphagocytic cells with large azurophilic cytoplasmic granules. NK cells express surface

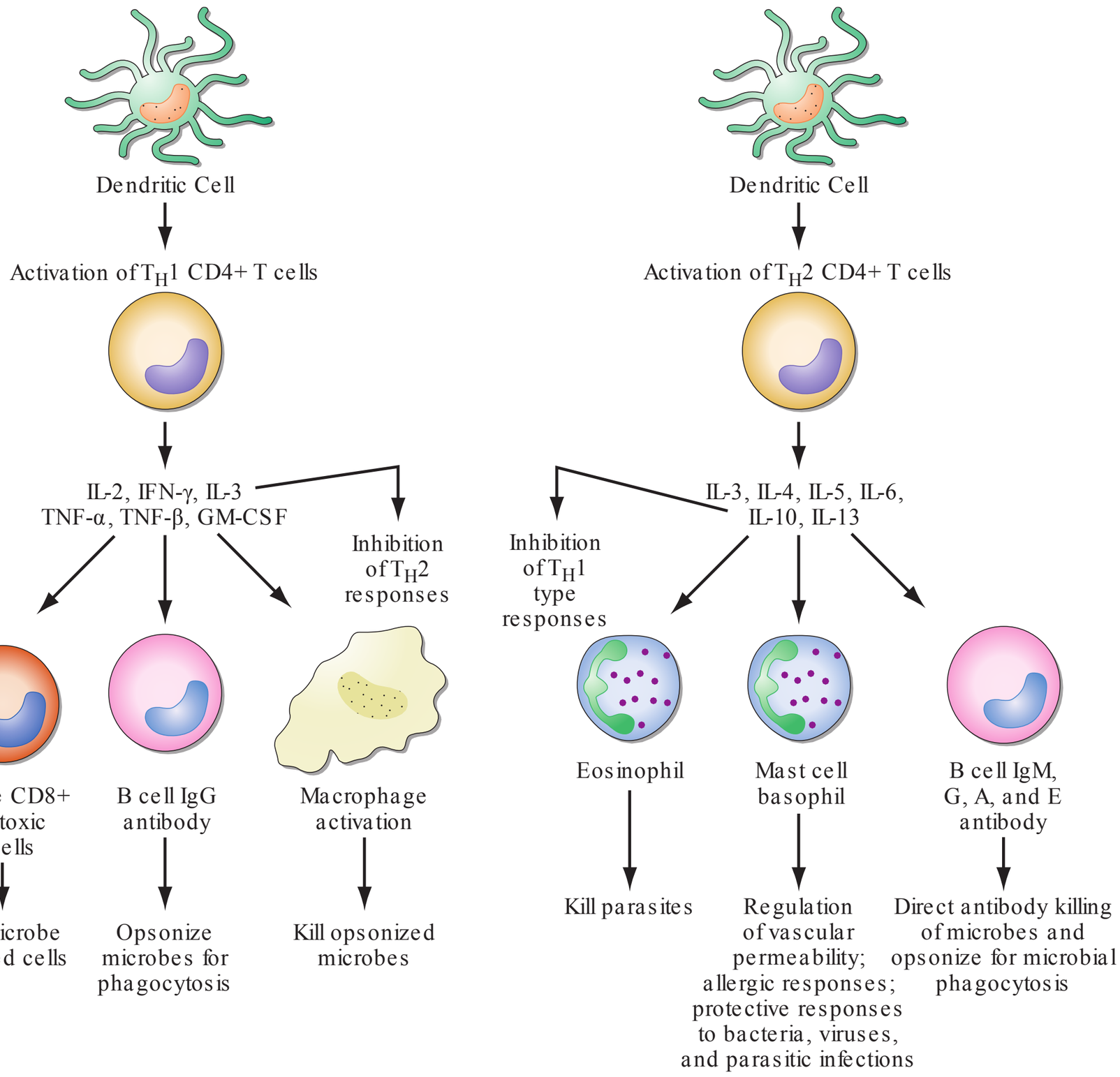


FIGURE 1-3

CD4+ helper T1 (T_H1) cells and T_H2 T cells secrete distinct but overlapping sets of cytokines. T_H1 CD4+ cells are frequently activated in immune and inflammatory reactions against intracellular bacteria or viruses, whereas T_H2 CD4+ cells are frequently activated for certain types of antibody production against parasites and extracellular encapsulated bacteria; they are also activated in allergic diseases. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor. (Adapted from S Romagnani: CD4 effector cells, in Inflammation: Basic Principles and Clinical Correlates, 3rd ed, J Gallin, R Snyderman [eds]. Philadelphia, Lippincott Williams & Wilkins, 1999, p 177; with permission.)

receptors for the Fc portion of IgG (FcR) (CD16) and for NCAM-I (CD56), and many NK cells express T lineage markers, particularly CD8, and proliferate in response to IL-2. NK cells arise in both bone marrow and thymic microenvironments.

Functionally, NK cells share features with both monocytes-macrophages and neutrophils in that they mediate both ADCC and NK cell activity. ADCC is the binding of an opsonized (antibody-coated) target cell to an Fc receptor-bearing effector cell via the Fc region of antibody, resulting in lysis of the target by the effector cell. NK cell cytotoxicity is the nonimmune (i.e., effector cell never having had previous contact with the target), MHC-unrestricted, non-antibody-mediated killing of target cells, which are usually malignant cell types, transplanted foreign cells, or virus-infected cells. Thus, NK cell cytotoxicity may play an important role in immune surveillance and destruction of malignant and virus-infected host cells. NK cell hyporesponsiveness is also observed in patients with Chédiak-Higashi syndrome, an autosomal recessive disease associated with fusion of cytoplasmic granules and defective degranulation of neutrophil lysosomes.

NK cells have a variety of surface receptors that have inhibitory or activating functions and belong to two structural families. These families include the immunoglobulin superfamily and the lectin-like type II transmembrane proteins. NK immunoglobulin superfamily receptors include the killer cell immunoglobulin-like activating or inhibitory receptors (KIRs), many of which have been shown to have HLA class I

ligands. The KIRs are made up proteins with either two (KIR2D) or three (KIR3D) extracellular immunoglobulin domains (D). Moreover, their nomenclature designates their function as either inhibitory KIRs with a long (L) cytoplasmic tail and immunoreceptor tyrosine-based inhibitory motif (ITIM) (KIRDL) or activating KIRs with a short (S) cytoplasmic tail (KIRDS). NK cell inactivation by KIRs is a central mechanism to prevent damage to normal host cells. Genetic studies have demonstrated the association of KIRs with viral infection outcome and autoimmune disease **(Table 1-10)**.

In addition to the KIRs, a second set of immunoglobulin superfamily receptors includes the natural cytotoxicity receptors (NCRs), which include NKp46, NKp30, and NKp44. These receptors help to mediate NK cell activation against target cells. The ligands to which NCRs bind on target cells have been recently recognized to be comprised of molecules of pathogens such as influenza, vaccinia, and malaria as well as host molecules expressed on tumor cells.

NK cell signaling is, therefore, a highly coordinated series of inhibiting and activating signals that prevent NK cells from responding to uninfected, nonmalignant self-cells; however, they are activated to attack malignant and virally infected cells **(Fig. 1-4)**. Recent evidence suggests that NK cells, although not possessing rearranging immune recognition genes, may be able to mediate recall for NK cell responses to viruses and for immune responses such as contact hypersensitivity.

Some NK cells express CD3 and invariant TCR-α chains and are termed NK T cells. TCRs of NK T cells recognize lipid molecules of intracellular bacteria when

TABLE 1-10

ASSOCIATION OF KIRS WITH DISEASE

DISEASE	KIR ASSOCIATION	OBSERVATION
Psoriatic arthritis	KIR2DS1/KIR2DS2; HLA-Cw group homozygosity	Susceptibility
Spondylarthritides	Increased KIR3DL2 expression Interaction HLA-B27 homodimers with KIR3DL1/KIR3DL2; independent of peptide	May contribute to disease pathology May contribute to disease pathogenesis
Ankylosing spondylitis	KIR3DL1/3DS1; HLA-B27 genotypes	Susceptibility
Rheumatoid vasculitis	KIR2DS2; HLA-Cw*03 Increased KIR2L2/2DS2 in patients with extraarticular manifestations	Susceptibility Clinical manifestations may have different genetic backgrounds with respect to KIR genotype
Rheumatoid arthritis	Decreased KIR2DS1/3DS1 in patients without bone erosions KIR2DS4; HLA-Cw4	Susceptibility Susceptibility
Scleroderma	KIR2DS2+/KIR2DL2–	Susceptibility
Behçet's disease	Altered KIR3DL1 expression	Associated with severe eye disease
Psoriasis vulgaris	2DS1; HLA-Cw*06 2DS1; 2DL5; haplotype B	Susceptibility Susceptibility
IDDM	KIR2DS2; HLA-C1	Susceptibility
Type 1 diabetes	KIR2DS2; HLA-C1 and no HLA-C2, no HLA-Bw4	Increased disease progression
Preeclampsia	KIR2DL1 with fewer KIR2DS (mother); HLA-C2 (fetus)	Increased disease progression
AIDS	KIR3DS1; HLA-Bw4Ile80 KIR3DS1 homozygous; no HLA-Bw4Ile^{80}	Decreased disease progression Increased disease progression
HCV infection	KIR2DL3 homozygous; HLA-C1 homozygous	Decreased disease progression
Cervical neoplasia (HPV induced)	KIR3DS1; HLA-C1 homozygous and no HLA-Bw4	Increased disease progression
Malignant melanoma	KIR2DL2 and/or KIR2DL3; HLA-C1	Increased disease progression

Abbreviations: HCV, hepatitis C virus; HLA, human leukocyte antigen; HPV, human papillomavirus; IDDM, insulin-dependent diabetes mellitus; KIR, killer cell immunoglobulin-like receptor.
Source: Adapted from R Diaz-Pena et al: Adv Exp Med Biol 649:286, 2009.

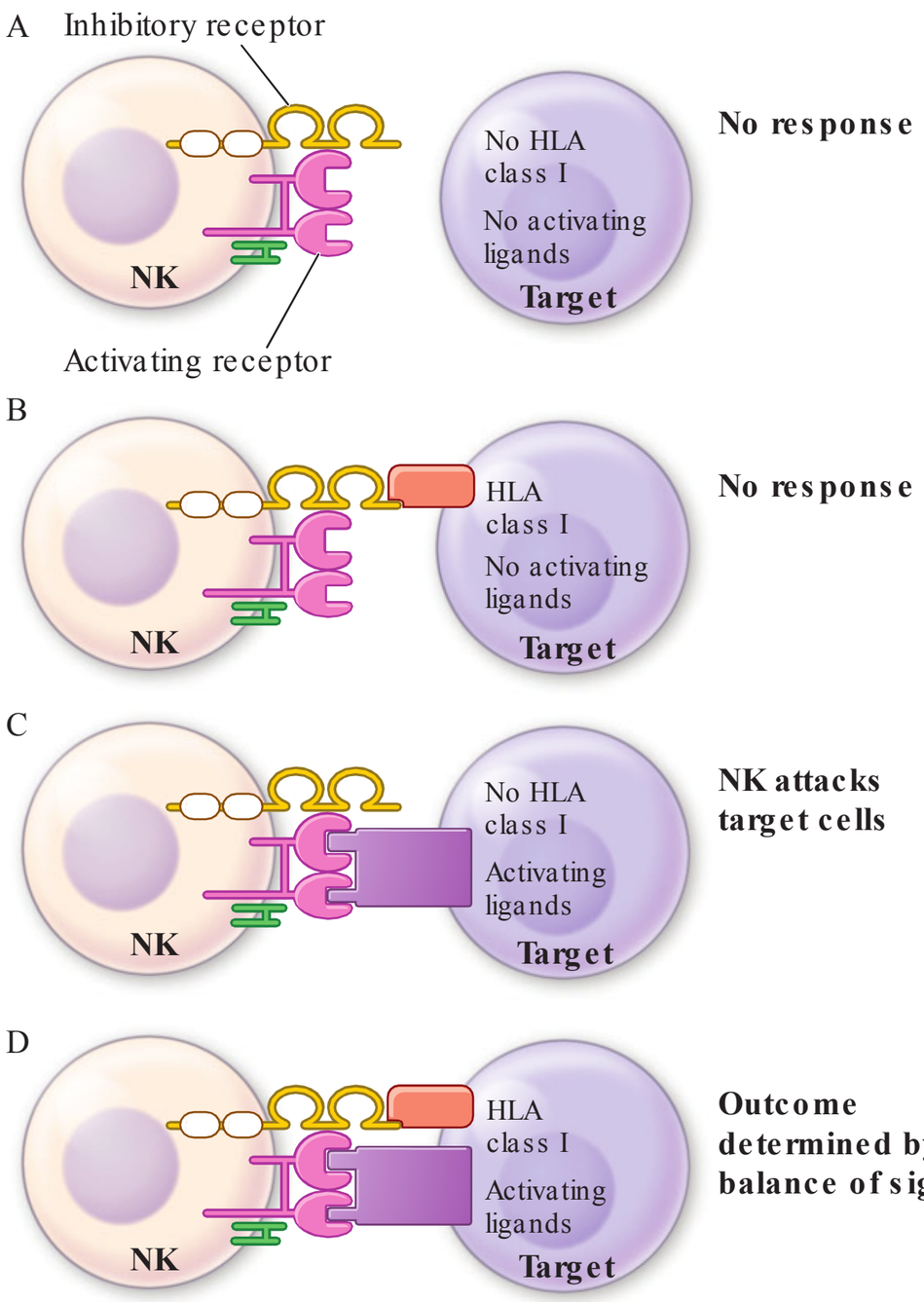


FIGURE 1-4

Encounters between NK cells: potential targets and possible outcomes. The amount of activating and inhibitory receptors on the NK cells and the amount of ligands on the target cell, as well as the qualitative differences in the signals transduced, determine the extent of the NK response. A. When target cells have no HLA class I or activating ligands, NK cells cannot kill target cells. B. When target cells bear self-HLA, NK cells cannot kill targets. C. When target cells are pathogen infected and have downregulated HLA and express activating ligands, NK cells kill target cells. D. When NK cells encounter targets with both self-HLA and activating receptors, then the level of target killing is determined by the balance of inhibitory and activating signals to the NK cell. HLA, human leukocyte antigen; NK, natural killer. (Adapted from LLanier: Annu Rev Immunol 23:225, 2005; reproduced with permission from Annual Reviews Inc. Copyright 2011 by Annual Reviews Inc.)

presented in the context of CD1d molecules on APCs. Upon activation, NK T cells secrete effector cytokines such as IL-4 and IFN-γ. This mode of recognition of intracellular bacteria such as Listeria monocytogenes and Mycobacterium tuberculosis by NK T cells leads to induction of activation of DCs and is thought to be an important innate defense mechanism against these organisms.

The receptors for the Fc portion of IgG (FcγRs) are present on NK cells, B cells, macrophages, neutrophils, and mast cells and mediate interactions of IgG with antibody-coated target cells, such as virally infected cells. Antibody-NK interaction via antibody Fc and NK cell FcR links the adaptive and innate immune systems and regulates the mediation of IgG antibody effector functions such as ADCC. There are both activation and inhibitory FcγRs. Activation FcRs, such as FcγRI (CD64), FcγRII (CD32), and FcγRII (CD64), are characterized by the presence of an immunoreceptor tyrosine-based activating motif (ITAM) sequence, whereas inhibitory FcRs, such as FcγRIIb, contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) sequence. There is evidence that dysregulation in IgG-FcγR interactions plays a role in arthritis, multiple sclerosis, and systemic lupus erythematosus.

Neutrophils, eosinophils, and basophils

Granulocytes are present in nearly all forms of inflammation and are amplifiers and effectors of innate immune responses (Figs. 1-2 and 1-3). Unchecked accumulation and activation of granulocytes can lead to host tissue damage, as seen in neutrophil- and eosinophil-mediated systemic necrotizing vasculitis. Granulocytes are derived from stem cells in bone marrow. Each type of granulocyte (neutrophil, eosinophil, or basophil) is derived from a different subclass of progenitor cell that is stimulated to proliferate by colony-stimulating factors (Table 1-7). During terminal maturation of granulocytes, class-specific nuclear morphology and cytoplasmic granules appear that allow for histologic identification of granulocyte type.

Neutrophils express Fc receptor IIIa for IgG (CD16) as well as receptors for activated complement components (C3b or CD35). Upon interaction of neutrophils with antibody-coated (opsonized) bacteria or immune complexes, azurophilic granules (containing myeloperoxidase, lysozyme, elastase, and other enzymes) and specific granules (containing lactoferrin, lysozyme, collagenase, and other enzymes) are released, and microbicidal superoxide radicals (O_2^-) are generated at the neutrophil surface. The generation of superoxide leads to inflammation by direct injury to tissue and by alteration of macromolecules such as collagen and DNA.

Eosinophils express Fc receptor II for IgG (CD32) and are potent cytotoxic effector cells for various parasitic organisms. In Nippostrongylus brasiliensis helminth infection, eosinophils are important cytotoxic effector cells for removal of these parasites. Key to regulation of eosinophil cytotoxicity to N. brasiliensis worms are antigen-specific T helper cells that produce IL-4, thus providing an example of regulation of innate immune responses by adaptive immunity antigen-specific T cells. Intracytoplasmic contents of eosinophils, such as major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, are capable of directly damaging tissues and may be responsible in part for the organ system dysfunction in the hypereosinophilic syndromes. Because the eosinophil granule contains

TABLE 1-11

EXAMPLES OF MEDIATORS RELEASED FROM IMMUNE CELLS AND BASOPHILS

MEDIATOR	ACTIONS
Histamine	Smooth-muscle contraction, increased vascular permeability
Slow reacting substance of anaphylaxis (SRSA) (leukotriene C_4, D_4, E_4)	Smooth-muscle contraction
Eosinophil chemotactic factor of anaphylaxis (ECF-A)	Chemotactic attraction of eosinophils
Platelet-activating factor	Activates platelets to secrete serotonin and other mediators: smooth-muscle contraction; induces vascular permeability
Neutrophil chemotactic factor (NCF)	Chemotactic attraction of neutrophils
Leukotactic activity (leukotriene B_4)	Chemotactic attraction of neutrophils
Heparin	Anticoagulant
Basophil kallikrein of anaphylaxis (BK-A)	Cleaves kininogen to form bradykinin

anti-inflammatory types of enzymes (histaminase, arylsulfatase, phospholipase D), eosinophils may homeostatically downregulate or terminate ongoing inflammatory responses.

Basophils and tissue mast cells are potent reservoirs of cytokines such as IL-4 and can respond to bacteria and viruses with antipathogen cytokine production through multiple TLRs expressed on their surface. Mast cells and basophils can also mediate immunity through the binding of antipathogen antibodies. This is a particularly important host defense mechanism against parasitic diseases. Basophils express high-affinity surface receptors for IgE (FcεRII) (CD23) and, upon cross-linking of basophil-bound IgE by antigen, can release histamine, eosinophil chemotactic factor of anaphylaxis, and neutral protease—all mediators of allergic immediate (anaphylaxis) hypersensitivity responses **(Table 1-11)**. In addition, basophils express surface receptors for activated complement components (C3a, C5a), through which mediator release can be directly affected. Thus, basophils, like most cells of the immune system, can be activated in the service of host defense against pathogens, or they can be activated for mediation release and cause pathogenic responses in allergic and inflammatory diseases.

The complement system

The complement system, an important soluble component of the innate immune system, is a series of plasma enzymes, regulatory proteins, and proteins that are activated in a cascading fashion, resulting in cell lysis. There are four pathways of the complement system: the classic activation pathway activated by antigen/antibody immune complexes, the mannose-binding lectin (MBL) (a serum collectin; Table 1-3) activation pathway activated by microbes with terminal mannose groups, the alternative activation pathway activated by microbes or tumor cells, and the terminal pathway that is common to the first three pathways and leads to the membrane attack complex that lyses cells **(Fig. 1-5)**. The series of enzymes of the complement system are serine proteases.

Activation of the classic complement pathway via immune complex binding to C1q links the innate and adaptive immune systems via specific antibody in the immune complex. The alternative complement activation pathway is antibody-independent and is activated by binding of C3 directly to pathogens and "altered self" such as tumor cells. In the renal glomerular inflammatory disease IgA nephropathy, IgA activates the alternative complement pathway and causes glomerular damage and decreased renal function. Activation of the classic complement pathway via C1, C4, and C2 and activation of the alternative pathway via factor D, C3, and factor B both lead to cleavage and activation of C3.

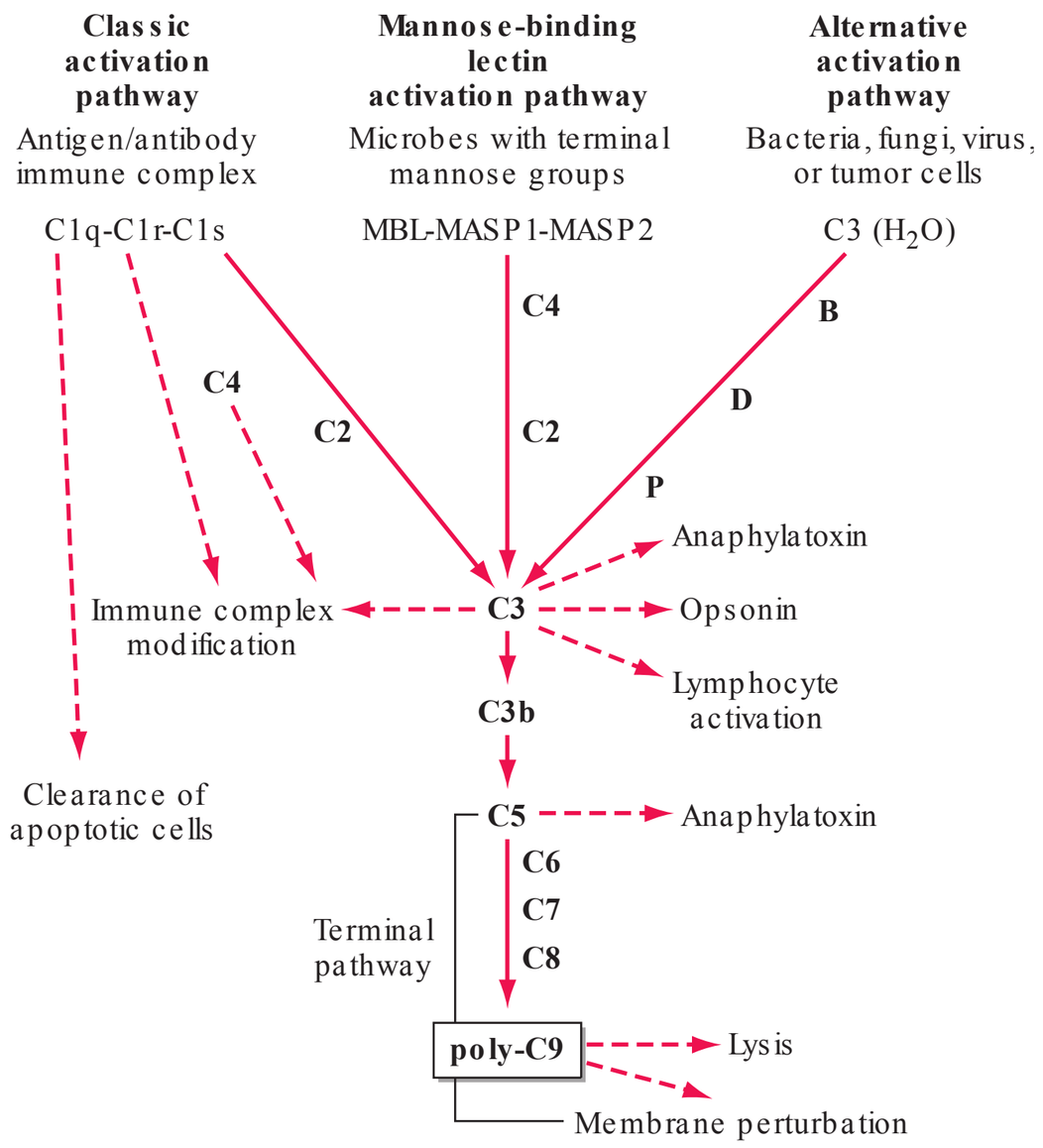


FIGURE 1-5

The four pathways and the effector mechanisms of the complement system. Dashed arrows indicate the functions of pathway components. (After BJ Morley, MJ Walport: The Complement Facts Books. London, Academic Press, 2000, Chap. 2; with permission. Copyright Academic Press, London, 2000.)

C3 activation fragments, when bound to target surfaces such as bacteria and other foreign antigens, are critical for opsonization (coating by antibody and complement) in preparation for phagocytosis. The MBL pathway substitutes MBL-associated serine proteases (MASPs) 1 and 2 for C1q, C1r, and C1s to activate C4. The MBL activation pathway is activated by mannose on the surface of bacteria and viruses.

The three pathways of complement activation all converge on the final common terminal pathway. C3 cleavage by each pathway results in activation of C5, C6, C7, C8, and C9, resulting in the membrane attack complex that physically inserts into the membranes of target cells or bacteria and lyses them.

Thus, complement activation is a critical component of innate immunity for responding to microbial infection. The functional consequences of complement activation by the three initiating pathways and the terminal pathway are shown in Fig. 1-5. In general the cleavage products of complement components facilitate microbe or damaged cell clearance (C1q, C4, C3), promote activation and enhancement of inflammation (anaphylatoxins, C3a, C5a), and promote microbe or opsonized cell lysis (membrane attack complex).

CYTOKINES

Cytokines are soluble proteins produced by a wide variety of cell types (Tables 1-7, **1-8**, and 1-9). They are critical for both normal innate and adaptive immune responses, and their expression may be perturbed in most immune, inflammatory, and infectious disease states.

Cytokines are involved in the regulation of the growth, development, and activation of immune system cells and in the mediation of the inflammatory response. In general, cytokines are characterized by considerable redundancy; different cytokines have similar functions. In addition, many cytokines are pleiotropic in that they are capable of acting on many different cell types. This pleiotropism results from the expression on multiple cell types of receptors for the same cytokine (see below), leading to the formation of "cytokine networks." The action of cytokines may be (1) autocrine when the target cell is the same cell that secretes the cytokine, (2) paracrine when the target cell is nearby, and (3) endocrine when the cytokine is secreted into the circulation and acts distal to the source.

Cytokines have been named based on presumed targets or based on presumed functions. Those cytokines that are thought to primarily target leukocytes have been named interleukins (IL-1, -2, -3, etc.). Many cytokines that were originally described as having a certain function have retained those names (e.g., granulocyte colony-stimulating factor [G-CSF]). Cytokines belong in general to three major structural families: the hematopoietin family; the TNF, IL-1, platelet-derived growth factor (PDGF), and transforming growth factor (TGF) β families; and the CXC and C-C chemokine families (Table 1-9). Chemokines are cytokines that regulate cell movement and trafficking; they act through G protein-coupled receptors and have a distinctive three-dimensional structure. IL-8 is the only chemokine that early on was named an IL (Table 1-7).

In general, cytokines exert their effects by influencing gene activation that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and the pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines that they secrete, which results in either humoral immune response (T_H2) or cell-mediated immune response (T_H1). A third type of T helper cell is the T_H17 cell that contributes to host defense against extracellular bacteria and fungi, particularly at mucosal sites (Fig. 1-2).

Cytokine receptors can be grouped into five general families based on similarities in their extracellular amino acid sequences and conserved structural domains. The immunoglobulin (Ig) super*f*amily represents a large number of cell-surface and secreted proteins. The IL-1 receptors (type 1, type 2) are examples of cytokine receptors with extracellular Ig domains.

The hallmark of the hematopoietic growth *f*actor (type 1) receptor family is that the extracellular regions of each receptor contain two conserved motifs. One motif, located at the N terminus, is rich in cysteine residues. The other motif is located at the C terminus proximal to the transmembrane region and comprises five amino acid residues, tryptophan-serine-X-tryptophan-serine (WSXWS). This family can be grouped on the basis of the number of receptor subunits they have and on the utilization of shared subunits. A number of cytokine receptors, i.e., IL-6, IL-11, IL-12, and leukemia inhibitory factor, are paired with gp130. There is also a common 150-kDa subunit shared by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. The gamma chain (γ_c) of the IL-2 receptor is common to the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors. Thus, the specific cytokine receptor is responsible for ligand-specific binding, whereas the subunits such as gp130, the 150-kDa subunit, and γ_c are important in signal transduction. The γ_c gene is on the X chromosome, and mutations in the γ_c protein result in the X-linked *f*orm o*f* severe combined immune de*f*iciency syndrome (X-SCID).

The members of the inter*f*eron (type II) receptor family include the receptors for IFN-γ and -β, which share a similar 210-amino-acid binding domain with conserved cysteine pairs at both the amino and carboxy termini. The members of the TNF (type III) receptor

*f*amily share a common binding domain composed of repeated cysteine-rich regions. Members of this family include the p55 and p75 receptors for TNF (TNF-R1 and TNF-R2, respectively); CD40 antigen, which is an important B cell-surface marker involved in immunoglobulin isotype switching; fas/Apo-1, whose triggering induces apoptosis; CD27 and CD30, which are found on activated T cells and B cells; and nerve growth factor receptor.

The common motif for the seven transmembrane helix *f*amily was originally found in receptors linked to GTP-binding proteins. This family includes receptors for chemokines (Table 1-8), β-adrenergic receptors, and retinal rhodopsin. It is important to note that two members of the chemokine receptor family, CXC chemokine receptor type 4 (CXCR4) and β chemokine receptor type 5 (CCR5), have been found to serve as the two major co-receptors for binding and entry of HIV into CD4-expressing host cells.

Significant advances have been made in defining the signaling pathways through which cytokines exert their intracellular effects. The Janus family of protein tyrosine kinases (JAK) is a critical element involved in signaling via the hematopoietin receptors. Four JAK kinases, JAK1, JAK2, JAK3, and Tyk2, preferentially bind different cytokine receptor subunits. Cytokine binding to its receptor brings the cytokine receptor subunits into apposition and allows a pair of JAKs to transphosphorylate and activate one another. The JAKs then phosphorylate the receptor on the tyrosine residues and allow signaling molecules to bind to the receptor, whereby the signaling molecules become phosphorylated. Signaling molecules bind the receptor because they have domains (SH2, or src homology 2 domains) that can bind phosphorylated tyrosine residues. There are a number of these important signaling molecules that bind the receptor, such as the adapter molecule SHC, which can couple the receptor to the activation of the mitogen-activated protein kinase pathway. In addition, an important class of substrate of the JAKs is the signal transducers and activators of transcription (STAT) family of transcription factors. STATs have SH2 domains that enable them to bind to phosphorylated receptors, where they are then phosphorylated by the JAKs. It appears that different STATs have specificity for different receptor subunits. The STATs then dissociate from the receptor and translocate to the nucleus, bind to DNA motifs that they recognize, and regulate gene expression. The STATs preferentially bind DNA motifs that are slightly different from one another and thereby control transcription of specific genes. The importance of this pathway is particularly relevant to lymphoid development. Mutations of JAK3 itself also result in a disorder identical to X-SCID; however, because JAK3 is found on chromosome 19 and not on the X chromosome, JAK3 deficiency occurs in boys and girls.

THE ADAPTIVE IMMUNE SYSTEM

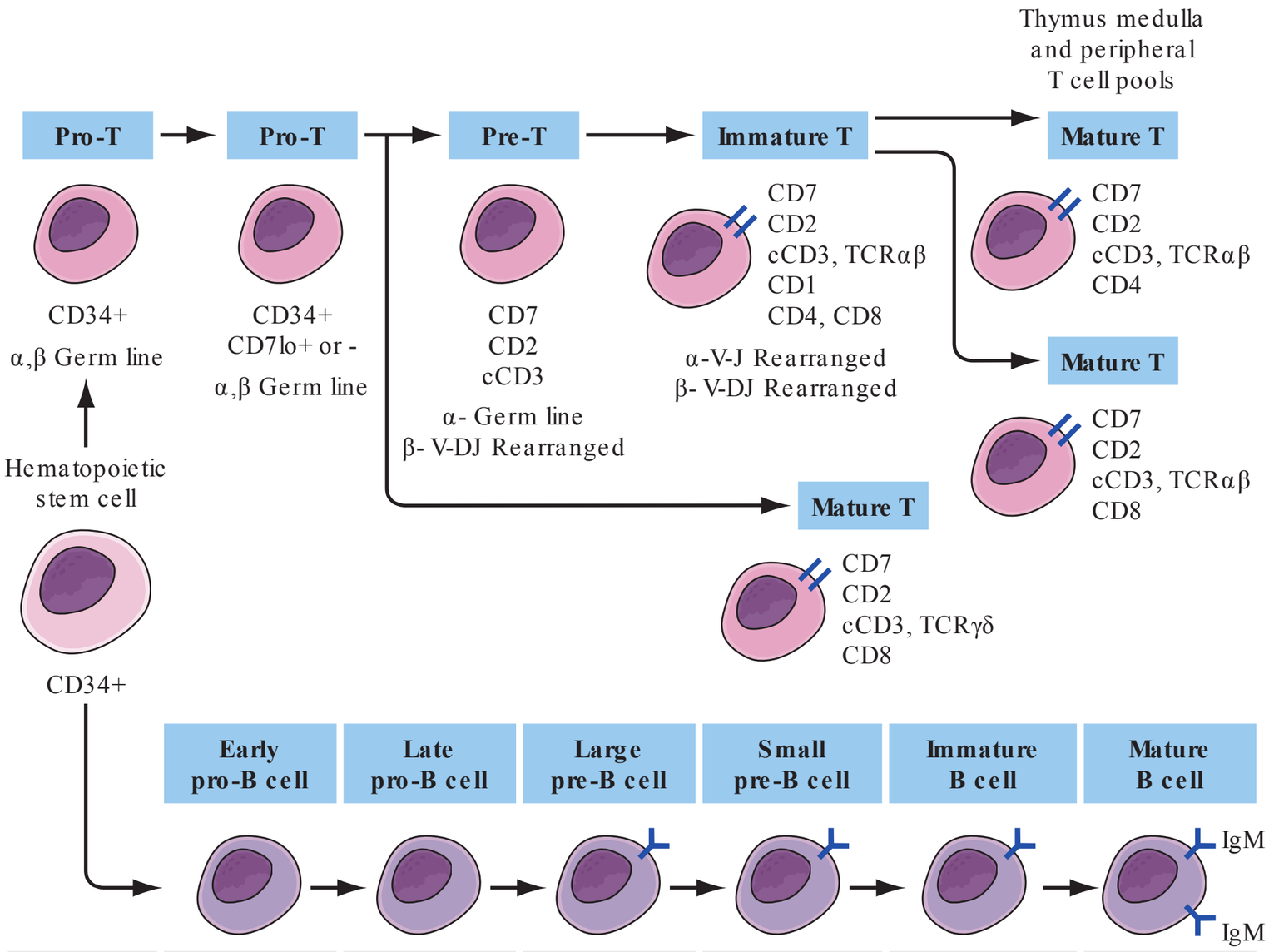
Adaptive immunity is characterized by antigen-specific responses to a foreign antigen or pathogen. A key feature of adaptive immunity is that following the initial contact with antigen (immunologic priming), subsequent antigen exposure leads to more rapid and vigorous immune responses (immunologic memory). The adaptive immune system consists of dual limbs of cellular and humoral immunity. The principal effectors of cellular immunity are T lymphocytes, whereas the principal effectors of humoral immunity are B lymphocytes. Both B and T lymphocytes derive from a common stem cell **(Fig. 1-6)**.

The proportion and distribution of immunocompetent cells in various tissues reflect cell traffic, homing patterns, and functional capabilities. Bone marrow is the major site of maturation of B cells, monocytes-macrophages, DCs, and granulocytes and contains pluripotent stem cells that, under the influence of various colony-stimulating factors, are capable of giving rise to all hematopoietic cell types. T cell precursors also arise from hematopoietic stem cells and home to the thymus for maturation. Mature T lymphocytes, B lymphocytes, monocytes, and DCs enter the circulation and home to peripheral lymphoid organs (lymph nodes, spleen) and mucosal surface-associated lymphoid tissue (gut, genitourinary, and respiratory tracts) as well as the skin and mucous membranes and await activation by foreign antigen.

T cells

The pool of effector T cells is established in the thymus early in life and is maintained throughout life both by new T cell production in the thymus and by antigen-driven expansion of virgin peripheral T cells into "memory" T cells that reside in peripheral lymphoid organs. The thymus exports ~2% of the total number of thymocytes per day throughout life, with the total number of daily thymic emigrants decreasing by ~3% per year during the first four decades of life.

Mature T lymphocytes constitute 70–80% of normal peripheral blood lymphocytes (only 2% of the total-body lymphocytes are contained in peripheral blood), 90% of thoracic duct lymphocytes, 30–40% of lymph node cells, and 20–30% of spleen lymphoid cells. In lymph nodes, T cells occupy deep paracortical areas around B cell germinal centers, and in the spleen, they are located in periarteriolar areas of white pulp. T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+ cytotoxic T cells capable of lysis of virus-infected or foreign cells (short-lived effector T cells) and CD4+ T cells capable of T cell help for CD8+ T cell and B cell development. Two populations of long-lived memory T cells are triggered by infections: effector memory and central memory



	Early pro-B cell	Late pro-B cell	Large pre-B cell	Small pre-B cell	Immature B cell	Mature B cell
High-chain genes	DJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
Low-chain genes	Germ line	Germ line	Germ line	VDJ rearranged	VDJ rearranged	VDJ rearranged
Surface Ig	Absent	Absent	μ H-chain at surface as part of pre-β receptor	μ H-chain in cytoplasm and at surface	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts
Surface marker proteins	CD34 CD10 CD19 CD38	CD10 CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD40	CD19 CD20 CD21 CD40

FIGURE 1-6

Development stages of T and B cells. Elements of the developing T and B cell receptor for antigen are shown schematically. The classification into the various stages of B cell development is primarily defined by rearrangement of the immunoglobulin (Ig) heavy (H) and light (L) chain genes and by the absence or presence of specific surface markers. The classification of stages of T cell development is primarily defined by cell-surface marker protein expression (sCD3, surface CD3 expression; cCD3, cytoplasmic CD3 expression; TCR, T cell receptor). (Adapted from CA Janeway et al [eds]: Immunobiology. The Immune Systemic Health and Disease, 4th ed. New York, Garland, 1999; with permission.)

T cells. Effector memory T cells reside in nonlymphoid organs and respond rapidly to repeated pathogenic infections with cytokine production and cytotoxic functions to kill virus-infected cells. Central memory T cells home to lymphoid organs where they replenish long- and short-lived and effector memory T cells as needed.

In general, CD4+ T cells are the primary regulatory cells of T and B lymphocyte and monocyte function by the production of cytokines and by direct cell contact (Fig. 1-2). In addition, T cells regulate erythroid cell maturation in bone marrow and, through cell contact (CD40 ligand), have an important role in activation of B cells and induction of Ig isotype switching. Considerable evidence now exists that colonization of the gut by commensal bacteria (the gut microbiome) is responsible for expansion of the peripheral CD4+ T cell compartment in normal children and adults.

Human T cells express cell-surface proteins that mark stages of intrathymic T cell maturation or identify specific functional subpopulations of mature T cells. Many of these molecules mediate or participate in important T cell functions (Table 1-1, Fig. 1-6).

The earliest identifiable T cell precursors in bone marrow are CD34+ pro-T cells (i.e., cells in which TCR genes are neither rearranged nor expressed). In the thymus, CD34+ T cell precursors begin cytoplasmic (c) synthesis of components of the CD3 complex of TCR-associated molecules (Fig. 1-6). Within T cell

precursors, TCR for antigen gene rearrangement yields two T cell lineages, expressing either TCR-αβ chains or TCR-γδ chains. T cells expressing the TCR-αβ chains constitute the majority of peripheral T cells in blood, lymph node, and spleen and terminally differentiate into either CD4+ or CD8+ cells. Cells expressing TCR-γδ chains circulate as a minor population in blood; their functions, although not fully understood, have been postulated to be those of immune surveillance at epithelial surfaces and cellular defenses against mycobacterial organisms and other intracellular bacteria through recognition of bacterial lipids.

In the thymus, the recognition of self-peptides on thymic epithelial cells, thymic macrophages, and DCs plays an important role in shaping the T cell repertoire to recognize foreign antigen (positive selection) and in eliminating highly autoreactive T cells (negative selection). As immature cortical thymocytes begin to express surface TCR for antigen, autoreactive thymocytes are destroyed (negative selection), thymocytes with TCRs capable of interacting with foreign antigen peptides in the context of self-MHC antigens are activated and develop to maturity (positive selection), and thymocytes with TCRs that are incapable of binding to self-MHC antigens die of attrition (no selection). Mature thymocytes that are positively selected are either CD4+ helper T cells or MHC class II–restricted cytotoxic (killer) T cells, or they are CD8+ T cells destined to become MHC class I–restricted cytotoxic T cells. MHC class I– or class II–restricted means that T cells recognize antigen peptide fragments only when they are presented in the antigen-recognition site of a class I or class II MHC molecule, respectively **(Chap. 2)**.

After thymocyte maturation and selection, CD4 and CD8 thymocytes leave the thymus and migrate to the peripheral immune system. The thymus continues to be a contributor to the peripheral immune system well into adult life, both normally and when the peripheral T cell pool is damaged, such as occurs in AIDS and cancer chemotherapy.

Molecular basis of T cell recognition of antigen

The TCR for antigen is a complex of molecules consisting of an antigen-binding heterodimer of either αβ or γδ chains noncovalently linked with five CD3 subunits (γ, δ, ε, ζ, and η) **(Fig. 1-7)**. The CD3 ζ chains are either disulfide-linked homodimers (CD3-ζ_2) or disulfide-linked heterodimers composed of one ζ chain and one η chain. TCR-αβ or TCR-γδ molecules must be associated with CD3 molecules to be inserted into the T cell-surface membrane, TCRα being paired with TCR-β and TCR-γ being paired with TCR-δ. Molecules of the CD3 complex mediate transduction of T cell activation signals via TCRs, whereas TCR-α and -β or -γ and -δ molecules combine to form the TCR antigen-binding site.

The α, β, γ, and δ TCR for antigen molecules have amino acid sequence homology and structural similarities to immunoglobulin heavy and light chains and are members of the immunoglobulin gene super*f*amily of molecules. The genes encoding TCR molecules are encoded as clusters of gene segments that rearrange during the course of T cell maturation. This creates an efficient and compact mechanism for housing the diversity requirements of antigen receptor molecules. The TCR-α chain is on chromosome 14 and consists of a series of V (variable), J (joining), and C (constant) regions. The TCR-β chain is on chromosome 7 and consists of multiple V, D (diversity), J, and C TCR-β loci. The TCR-γ chain is on chromosome 7, and the TCR-δ chain is in the middle of the TCR-α locus on chromosome 14. Thus, molecules of the TCR for antigen have constant (framework) and variable regions, and the gene segments encoding the α, β, γ, and δ chains of these molecules are recombined and selected in the thymus, culminating in synthesis of the completed molecule. In both T and B cell precursors (see below), DNA rearrangements of antigen receptor genes involve the same enzymes, recombinase activating gene (RAG) 1 and RAG2, both DNA-dependent protein kinases.

TCR diversity is created by the different V, D, and J segments that are possible for each receptor chain by the many permutations of V, D, and J segment combinations, by "N-region diversification" due to the addition of nucleotides at the junction of rearranged gene segments, and by the pairing of individual chains to form a TCR dimer. As T cells mature in the thymus, the repertoire of antigen-reactive T cells is modified by selection processes that eliminate many autoreactive T cells, enhance the proliferation of cells that function appropriately with self-MHC molecules and antigen, and allow T cells with nonproductive TCR rearrangements to die.

TCR-αβ cells do not recognize native protein or carbohydrate antigens. Instead, T cells recognize only short (~9–13 amino acids) peptide fragments derived from protein antigens taken up or produced in APCs. Foreign antigens may be taken up by endocytosis into acidified intracellular vesicles or by phagocytosis and degraded into small peptides that associate with MHC class II molecules (exogenous antigen-presentation pathway). Other foreign antigens arise endogenously in the cytosol (such as from replicating viruses) and are broken down into small peptides that associate with MHC class I molecules (endogenous antigen-presenting pathway). Thus, APCs proteolytically degrade foreign proteins and display peptide fragments embedded in the MHC class I or II antigen-recognition site on the MHC molecule surface, where foreign peptide fragments are available to bind to TCR-αβ or TCR-γδ chains of reactive T cells. CD4 molecules act as adhesives and, by direct binding to MHC class II (DR,

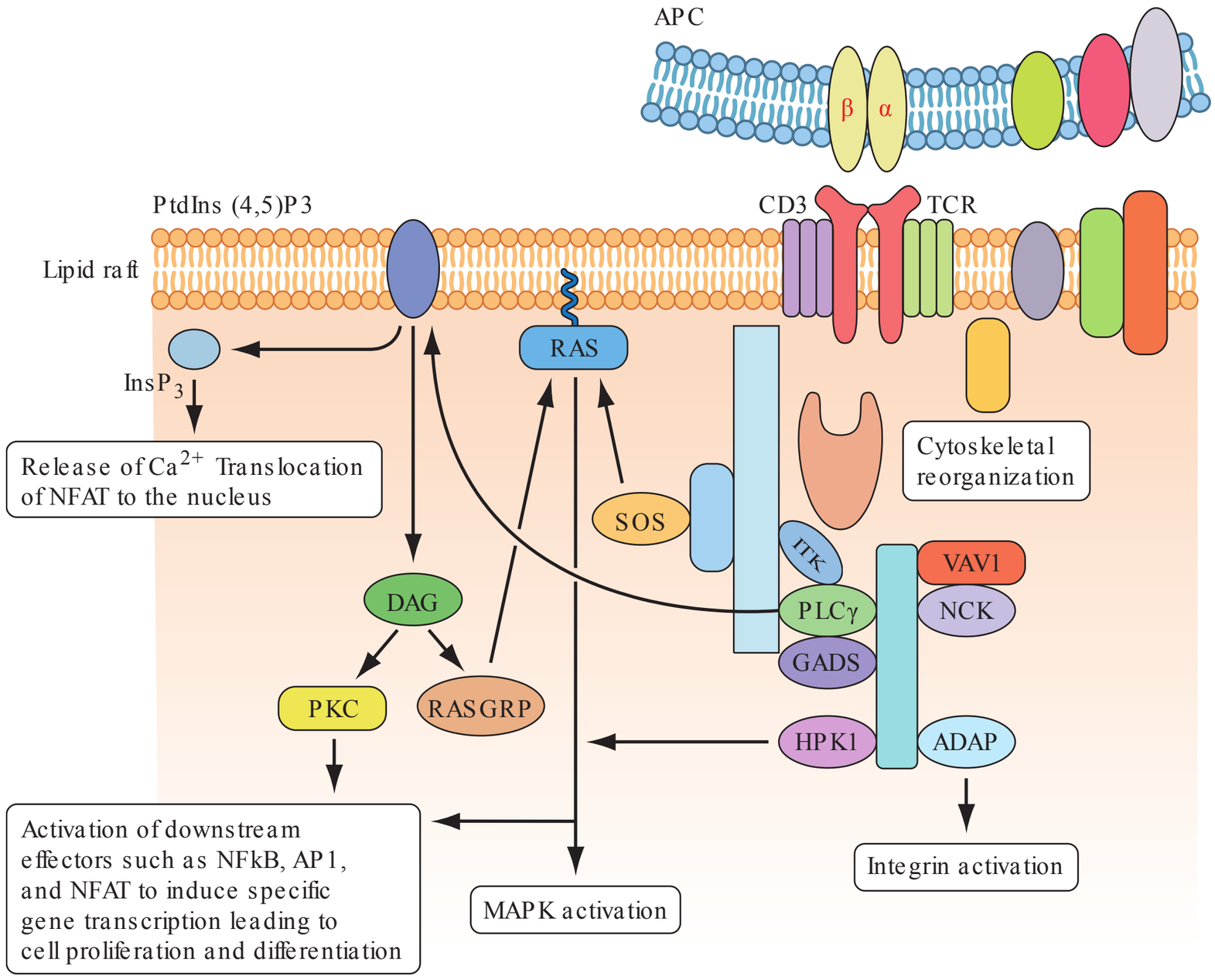


FIGURE 1-7

Signaling through the T cell receptor. Activation signals are mediated via immunoreceptor tyrosine-based activation (ITAM) sequences in LAT and CD3 chains (blue bars) that bind to enzymes and transduce activation signals to the nucleus via the indicated intracellular activation pathways. Ligation of the T cell receptor (TCR) by MHC complexed with antigen results in sequential activation of LCK and γ-chain-associated protein kinase of 70 kDa (ZAP-70). ZAP-70 phosphorylates several downstream targets, including LAT (linker for activation of T cells) and SLP76 (SCR homology 2 [SH2] domain-containing leukocyte protein of 76 kDa). SLP76 is recruited to membrane-bound LAT through its constitutive interaction with GADS (GRB2-related adaptor protein). Together, SLP76 and LAT nucleate a multimolecular signaling complex, which induces a host of downstream responses, including calcium flux, mitogen-activated protein kinase (MAPK) activation, integrin activation, and cytoskeletal reorganization. APC, antigen-presenting cell. (Adapted from GA Koretzky et al: Nat Rev Immunol 6:67, 2006; with permission from Macmillan Publishers Ltd. Copyright 2006.)

DQ, or DP) molecules, stabilize the interaction of TCR with peptide antigen (Fig. 1-7). Similarly, CD8 molecules also act as adhesives to stabilize the TCR-antigen interaction by direct CD8 molecule binding to MHC class I (A, B, or C) molecules.

Antigens that arise in the cytosol and are processed via the endogenous antigen-presentation pathway are cleaved into small peptides by a complex of proteases called the proteasome. From the proteasome, antigen peptide fragments are transported from the cytosol into the lumen of the endoplasmic reticulum by a heterodimeric complex termed transporters associated with antigen processing, or TAP proteins. There, MHC class I molecules in the endoplasmic reticulum membrane physically associate with processed cytosolic peptides. Following peptide association with class I molecules, peptide-class I complexes are exported to the Golgi apparatus, and then to the cell surface, for recognition by CD8+ T cells.

Antigens taken up from the extracellular space via endocytosis into intracellular acidified vesicles are degraded by vesicle proteases into peptide fragments. Intracellular vesicles containing MHC class II molecules fuse with peptide-containing vesicles, thus allowing peptide fragments to physically bind to MHC class II molecules. Peptide-MHC class II complexes are then transported to the cell surface for recognition by CD4+ T cells **(Chap. 2)**.

Whereas it is generally agreed that the TCR-αβ receptor recognizes peptide antigens in the context of MHC class I or class II molecules, lipids in the cell wall of intracellular bacteria such as M. tuberculosis can also be presented to a wide variety of T cells, including subsets of TCR-γδ T cells, and a subset of CD8+ TCR-αβ T cells. Importantly, bacterial lipid antigens are not presented in the context of MHC class I or II molecules, but rather are presented in the context of MHC-related CD1 molecules. Some γδ T cells that recognize lipid

antigens via CD1 molecules have very restricted TCR usage, do not need antigen priming to respond to bacterial lipids, and may actually be a form of innate rather than acquired immunity to intracellular bacteria.

Just as foreign antigens are degraded and their peptide fragments presented in the context of MHC class I or class II molecules on APCs, endogenous self-proteins also are degraded, and self-peptide fragments are presented to T cells in the context of MHC class I or class II molecules on APCs. In peripheral lymphoid organs, there are T cells that are capable of recognizing self-protein fragments but normally are anergic or tolerant, i.e., nonresponsive to self-antigenic stimulation, due to lack of self-antigen upregulating APC co-stimulatory molecules such as B7-1 (CD80) and B7-2 (CD86) (see below).

Once engagement of mature T cell TCR by foreign peptide occurs in the context of self-MHC class I or class II molecules, binding of non-antigen-specific adhesion ligand pairs such as CD54-CD11/CD18 and CD58-CD2 stabilizes MHC peptide-TCR binding, and the expression of these adhesion molecules is upregulated (Fig. 1-7). Once antigen ligation of the TCR occurs, the T cell membrane is partitioned into lipid membrane microdomains, or lipid ra*fts*, that coalesce the key signaling molecules TCR/CD3 complex, CD28, CD2, LAT (linker for activation of T cells), intracellular activated (dephosphorylated) src family protein tyrosine kinases (PTKs), and the key CD3ζ-associated protein-70 (ZAP-70) PTK (Fig. 1-7). Importantly, during T cell activation, the CD45 molecule, with protein tyrosine phosphatase activity, is partitioned away from the TCR complex to allow activating phosphorylation events to occur. The coalescence of signaling molecules of activated T lymphocytes in microdomains has suggested that T cell-APC interactions can be considered immunologic synapses, analogous in function to neuronal synapses.

After TCR-MHC binding is stabilized, activation signals are transmitted through the cell to the nucleus and lead to the expression of gene products important in mediating the wide diversity of T cell functions such as the secretion of IL-2. The TCR does not have intrinsic signaling activity but is linked to a variety of signaling pathways via immunoreceptor tyrosine-based activation motifs (ITAMs) expressed on the various CD3 chains that bind to proteins that mediate signal transduction. Each of the pathways results in the activation of particular transcription factors that control the expression of cytokine and cytokine receptor genes. Thus, antigen-MHC binding to the TCR induces the activation of the src family of PTKs, fyn and lck (lck is associated with CD4 or CD8 co-stimulatory molecules); phosphorylation of CD3ζ chain; activation of the related tyrosine kinases ZAP-70 and syk; and downstream activation of the calcium-dependent calcineurin pathway, the ras pathway, and the protein kinase C pathway. Each of these pathways leads to activation of specific families of transcription factors (including NF-AT, fos and jun, and rel/NF-κB) that form heteromultimers capable of inducing expression of IL-2, IL-2 receptor, IL-4, TNF-α, and other T cell mediators.

In addition to the signals delivered to the T cell from the TCR complex and CD4 and CD8, molecules on the T cell, such as CD28 and inducible co-stimulator (ICOS), and molecules on DCs, such as B7-1 (CD80) and B7-2 (CD86), also deliver important co-stimulatory signals that upregulate T cell cytokine production and are essential for T cell activation. If signaling through CD28 or ICOS does not occur, or if CD28 is blocked, the T cell becomes anergic rather than activated (see "Immune Tolerance and Autoimmunity" on p. 34). CTLA-4 (CD152) is similar to CD28 in its ability to bind CD80 and CD86. Unlike CD28, CTLA-4 transmits an inhibitory signal to T cells, acting as an off switch.

T cell exhaustion in viral infections and cancer

In chronic viral infections such as HIV-1, hepatitis C virus, and hepatitis B virus and in chronic malignancies, the persistence of antigen disrupts memory T cell function, resulting in defects in memory T cell responses. This has been defined as T cell exhaustion and is associated with T cell programmed cell death protein 1 (PD-1) (CD279) expression. Exhausted T cells have compromised proliferation and lose the ability to produce effector molecules, like IL-2, TNF-α, and IFN-γ. PD-1 downregulates T cell responses and is associated with T cell exhaustion and disease progression. For this reason, inhibition of T cell PD-1 activity to enhance effector T cell function is being explored as a target for immunotherapy in both viral infections and certain malignancies.

T cell superantigens

Conventional antigens bind to MHC class I or II molecules in the groove of the αβ heterodimer and bind to T cells via the V regions of the TCR-α and -β chains. In contrast, superantigens bind directly to the lateral portion of the TCR-β chain and MHC class II β chain and stimulate T cells based solely on the Vβ gene segment used independent of the D, J, and Vα sequences present. Superantigens are protein molecules capable of activating up to 20% of the peripheral T cell pool, whereas conventional antigens activate <1 in 10,000 T cells. T cell superantigens include staphylococcal enterotoxins and other bacterial products. Superantigen stimulation of human peripheral T cells occurs in the clinical setting of staphylococcal toxic shock syndrome, leading to massive overproduction of T cell cytokines that leads to hypotension and shock.

B cells

Mature B cells constitute 10–15% of human peripheral blood lymphocytes, 20–30% of lymph node cells, 50% of splenic lymphocytes, and ~10% of bone marrow

lymphocytes. B cells express on their surface intramembrane immunoglobulin (Ig) molecules that function as B cell receptors (BCRs) for antigen in a complex of Ig-associated α and β signaling molecules with properties similar to those described in T cells **(Fig. 1-8)**. Unlike T cells, which recognize only processed peptide fragments of conventional antigens embedded in the notches of MHC class I and class II antigens of APCs, B cells are capable of recognizing and proliferating to whole unprocessed native antigens via antigen binding to B cell–surface Ig (sIg) receptors. B cells also express surface receptors for the Fc region of IgG molecules (CD32) as well as receptors for activated complement components (C3d or CD21, C3b or CD35). The primary function of B cells is to produce antibodies. B cells also serve as APCs and are highly efficient at antigen processing. Their antigen-presenting function is enhanced by a variety of cytokines. Mature B cells are derived from bone marrow precursor cells that arise continuously throughout life (Fig. 1-6).

B lymphocyte development can be separated into antigen-independent and antigen-dependent phases. Antigen-independent B cell development occurs in primary lymphoid organs and includes all stages of B cell maturation up to the sIg+ mature B cell. Antigen-dependent B cell maturation is driven by the interaction of antigen with the mature B cell sIg, leading to memory B cell induction, Ig class switching, and plasma cell formation. Antigen-dependent stages of B cell maturation occur in secondary lymphoid organs, including lymph node, spleen, and gut Peyer's patches. In contrast to the T cell repertoire that is generated intrathymically

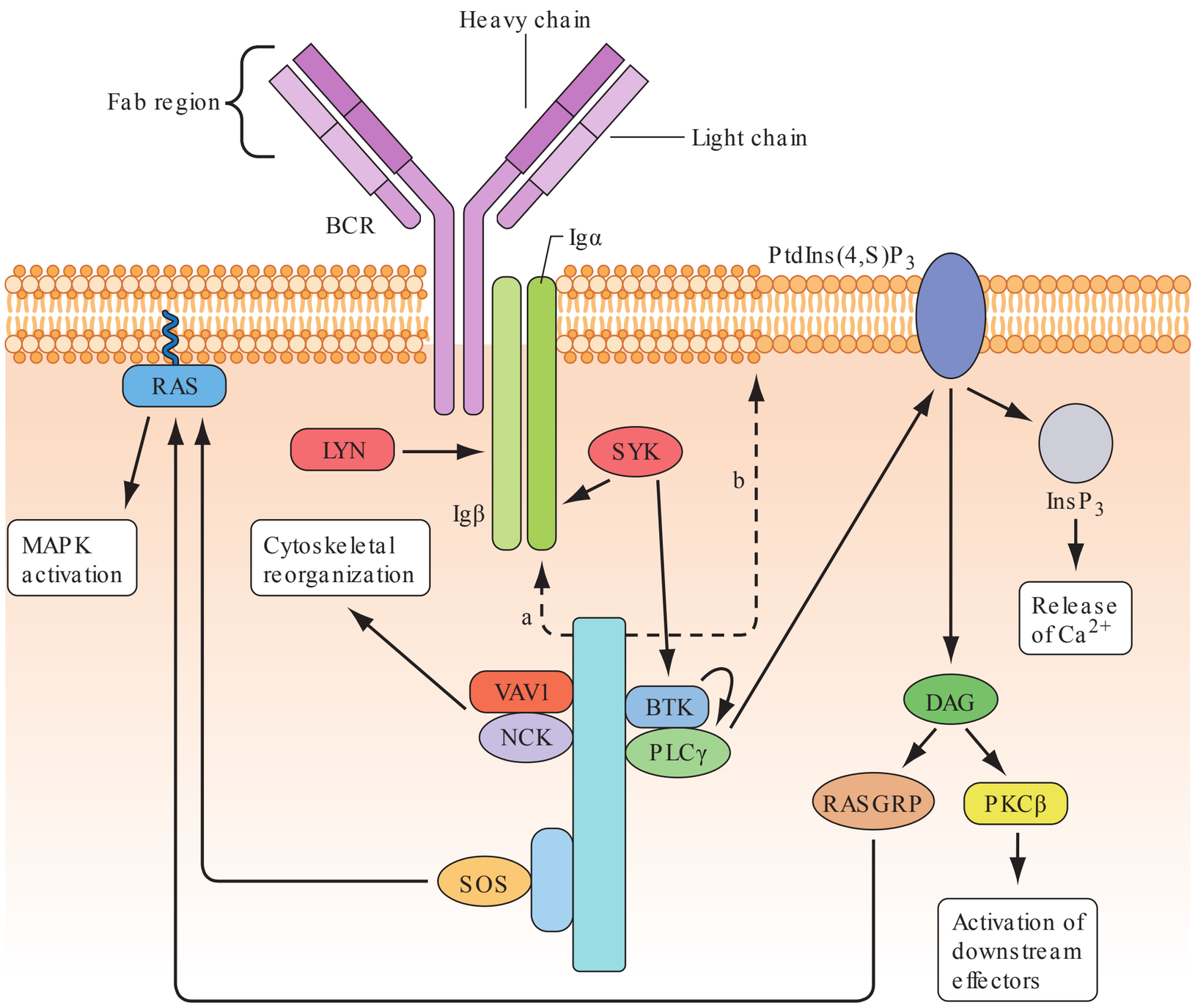


FIGURE 1-8

B cell receptor (BCR) activation results in the sequential activation of protein tyrosine kinases, which results in the formation of a signaling complex and activation of downstream pathways as shown. Whereas SLP76 is recruited to the membrane through GADS and LAT, the mechanism of SLP65 recruitment is unclear. Studies have indicated two mechanisms: (a) direct binding by the SH2 domain of SLP65 to immunoglobulin (Ig) of the BCR complex or (b) membrane recruitment through a leucine zipper in the amino terminus of SLP65 and an unknown binding partner. ADAP, adhesion- and degranulation-promoting adaptor protein; AP1, activator protein 1; BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; GRB2, growth factor receptor-bound protein 2; HPK1, hematopoietic progenitor kinase 1; $InsP_3$, inositol-1,4,5-trisphosphate; ITK, interleukin-2-inducible T cell kinase; NCK, noncatalytic region of tyrosine kinase; NF-B, nuclear factor B; PKC, protein kinase C; PLC, phospholipase C; $PtdIns(4,5)P_2$, phosphatidylinositol-4,5-bisphosphate; RASGRP, RAS guanyl-releasing protein; SOS, son of sevenless homologue; SYK, spleen tyrosine kinase. (Adapted from GA Koretzky et al: Nat Rev Immunol 6:67, 2006; with permission from Macmillan Publishers Ltd. Copyright 2006.)

before contact with foreign antigen, the repertoire of B cells expressing diverse antigen-reactive sites is modified by further alteration of Ig genes after stimulation by antigen—a process called somatic hypermutation—that occurs in lymph node germinal centers.

During B cell development, diversity of the antigen-binding variable region of Ig is generated by an ordered set of Ig gene rearrangements that are similar to the rearrangements undergone by TCR α, β, γ, and δ genes. For the heavy chain, there is first a rearrangement of D segments to J segments, followed by a second rearrangement between a V gene segment and the newly formed D-J sequence; the C segment is aligned to the V-D-J complex to yield a functional Ig heavy chain gene (V-D-J-C). During later stages, a functional κ or γ light chain gene is generated by rearrangement of a V segment to a J segment, ultimately yielding an intact Ig molecule composed of heavy and light chains.

The process of Ig gene rearrangement is regulated and results in a single antibody specificity produced by each B cell, with each Ig molecule comprising one type of heavy chain and one type of light chain. Although each B cell contains two copies of Ig light and heavy chain genes, only one gene of each type is productively rearranged and expressed in each B cell, a process termed allelic exclusion.

There are ~300 V_κ genes and 5 J_κ genes, resulting in the pairing of V_κ and J_κ genes to create >1500 different kappa light chain combinations. There are ~70 V_λ genes and $4J_\lambda$ genes for >280 different lambda light chain combinations. The number of distinct light chains that can be generated is increased by somatic mutations within the V and J genes, thus creating large numbers of possible specificities from a limited amount of germline genetic information. As noted above, in heavy chain Ig gene rearrangement, the VH domain is created by the joining of three types of germline genes called V_H, D_H, and J_H, thus allowing for even greater diversity in the variable region of heavy chains than of light chains.

The most immature B cell precursors (early pro-B cells) lack cytoplasmic Ig (cIg) and sIg (Fig. 1-6). The large pre-B cell is marked by the acquisition of the surface pre-BCR composed of μ heavy (H) chains and a pre-B light chain, termed ψLC. ψLC is a surrogate light chain receptor encoded by the nonrearranged V pre-B and the γ5 light chain locus (the pre-BCR). Pro- and pre-B cells are driven to proliferate and mature by signals from bone marrow stroma—in particular, IL-7. Light chain rearrangement occurs in the small pre-B cell stage such that the full BCR is expressed at the immature B cell stage. Immature B cells have rearranged Ig light chain genes and express sIgM. As immature B cells develop into mature B cells, sIgD is expressed as well as sIgM. At this point, B lineage development in bone marrow is complete, and B cells exit into the peripheral circulation and migrate to secondary lymphoid organs to encounter specific antigens.

Random rearrangements of Ig genes occasionally generate self-reactive antibodies, and mechanisms must be in place to correct these mistakes. One such mechanism is BCR editing, whereby autoreactive BCRs are mutated to not react with self-antigens. If receptor editing is unsuccessful in eliminating autoreactive B cells, then autoreactive B cells undergo negative selection in the bone marrow through induction of apoptosis after BCR engagement of self-antigen.

After leaving the bone marrow, B cells populate peripheral B cell sites, such as lymph node and spleen, and await contact with foreign antigens that react with each B cell's clonotypic receptor. Antigen-driven B cell activation occurs through the BCR, and a process known as somatic hypermutation takes place whereby point mutations in rearranged H- and L-genes give rise to mutant sIg molecules, some of which bind antigen better than the original sIg molecules. Somatic hypermutation, therefore, is a process whereby memory B cells in peripheral lymph organs have the best binding, or the highest-affinity antibodies. This overall process of generating the best antibodies is called af nity maturation *of* antibody.

Lymphocytes that synthesize IgG, IgA, and IgE are derived from sIgM+, sIgD+ mature B cells. Ig class switching occurs in lymph node and other peripheral lymphoid tissue germinal centers. CD40 on B cells and CD40 ligand on T cells constitute a critical costimulatory receptor-ligand pair of immune-stimulatory molecules. Pairs of CD40+ B cells and CD40 ligand+ T cells bind and drive B cell Ig class switching via T cell-produced cytokines such as IL-4 and TGF-β. IL-1, -2, -4, -5, and -6 synergize to drive mature B cells to proliferate and differentiate into Ig-secreting cells.

Humoral mediators of adaptive immunity: immunoglobulins

Immunoglobulins are the products of differentiated B cells and mediate the humoral arm of the immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or other foreign substance from the body. The structural basis of Ig molecule function and Ig gene organization has provided insight into the role of antibodies in normal protective immunity, pathologic immune-mediated damage by immune complexes, and autoantibody formation against host determinants.

All immunoglobulins have the basic structure of two heavy and two light chains (Fig. 1-8). Immunoglobulin isotype (i.e., G, M, A, D, E) is determined by the type of Ig heavy chain present. IgG and IgA isotypes can be divided further into subclasses (G1, G2, G3, G4, and

A1, A2) based on specific antigenic determinants on Ig heavy chains. The characteristics of human immunoglobulins are outlined in **Table 1-12**. The four chains are covalently linked by disulfide bonds. Each chain is made up of a V region and C regions (also called domains), themselves made up of units of ~110 amino acids. Light chains have one variable (V_L) and one constant (C_L) unit; heavy chains have one variable unit (V_H) and three or four constant (C_H) units, depending on isotype. As the name suggests, the constant, or C, regions of Ig molecules are made up of homologous sequences and share the same primary structure as all other Ig chains of the same isotype and subclass. Constant regions are involved in biologic functions of Ig molecules. The C_H2 domain of IgG and the C_H4 units of IgM are involved with the binding of the C1q portion of C1 during complement activation. The C_H region at the carboxy-terminal end of the IgG molecule, the Fc region, binds to surface Fc receptors (CD16, CD32, CD64) of macrophages, DCs, NK cells, B cells, neutrophils, and eosinophils. The Fc of IgA binds to FcαR (CD89), and the Fc of IgE binds to FcεR (CD23).

Variable regions (V_L and V_H) constitute the antibody-binding (Fab) region of the molecule. Within the V_L and V_H regions are hypervariable regions (extreme sequence variability) that constitute the antigen-binding site unique to each Ig molecule. The idiotype is defined as the specific region of the Fab portion of the Ig molecule to which antigen binds. Antibodies against the idiotype portion of an antibody molecule are called anti-idiotype antibodies. The formation of such antibodies in vivo during a normal B cell antibody response may generate a negative (or "off") signal to B cells to terminate antibody production.

IgG constitutes ~75–85% of total serum immunoglobulin. The four IgG subclasses are numbered in order of their level in serum, IgG1 being found in greatest amounts and IgG4 the least. IgG subclasses have clinical relevance in their varying ability to bind macrophage and neutrophil Fc receptors and to activate

TABLE 1-12

PHYSICAL, CHEMICAL, AND BIOLOGIC PROPERTIES OF HUMAN IMMUNOGLOBULINS

PROPERTY	IGG	IGA	IGM	IGD	IGE
Usual molecular form	Monomer	Monomer, dimer	Pentamer, hexamer	Monomer	Monomer
Other chains	None	J chain, SC	J chain	None	None
Subclasses	G1, G2, G3, G4	A1, A2	None	None	None
Heavy chain allotypes	Gm (=30)	No A1, A2m (2)	None	None	None
Molecular mass, kDa	150	160, 400	950, 1150	175	190
Serum level in average adult, mg/mL	9.5–12.5	1.5–2.6	0.7–1.7	0.04	0.0003
Percentage of total serum Ig	75–85	7–15	5–10	0.3	0.019
Serum half-life, days	23	6	5	3	2.5
Synthesis rate, mg/kg per day	33	65	7	0.4	0.016
Antibody valence	2	2, 4	10, 12	2	2
Classical complement activation	+(G1, 2?, 3)	–	++	–	–
Alternate complement activation	+(G4)	+	–	+	–
Binding cells via Fc	Macrophages, neutrophils, large granular lymphocytes	Lymphocytes	Lymphocytes	None	Mast cells, basophils, B cells
Biologic properties	Placental transfer, secondary Ab for most antipathogen responses	Secretory immunoglobulin	Primary Ab responses	Marker for mature B cells	Allergy, antiparasite responses

Source: After L Carayannopoulos, JD Capra, in WE Paul (ed): Fundamental Immunology, 3rd ed. New York, Raven, 1993; with permission.

complement (Table 1-12). Moreover, selective deficiencies of certain IgG subclasses give rise to clinical syndromes in which the patient is inordinately susceptible to bacterial infections. IgG antibodies are frequently the predominant antibody made after rechallenge of the host with antigen (secondary antibody response).

IgM antibodies normally circulate as a 950-kDa pentamer with 160-kDa bivalent monomers joined by a molecule called the J chain, a 15-kDa nonimmunoglobulin molecule that also effects polymerization of IgA molecules. IgM is the first immunoglobulin to appear in the immune response (primary antibody response) and is the initial type of antibody made by neonates. Membrane IgM in the monomeric form also functions as a major antigen receptor on the surface of mature B cells (Table 1-12). IgM is an important component of immune complexes in autoimmune diseases. For example, IgM antibodies against IgG molecules (rheumatoid factors) are present in high titers in rheumatoid arthritis, other collagen diseases, and some infectious diseases (subacute bacterial endocarditis).

IgA constitutes only 7–15% of total serum immunoglobulin but is the predominant class of immunoglobulin in secretions. IgA in secretions (tears, saliva, nasal secretions, gastrointestinal tract fluid, and human milk) is in the form of secretory IgA (sIgA), a polymer consisting of two IgA monomers, a joining molecule, again called the J chain, and a glycoprotein called the secretory protein. Of the two IgA subclasses, IgA1 is primarily found in serum, whereas IgA2 is more prevalent in secretions. IgA fixes complement via the alternative complement pathway and has potent antiviral activity in humans by prevention of virus binding to respiratory and gastrointestinal epithelial cells.

IgD is found in minute quantities in serum and, together with IgM, is a major receptor for antigen on the naïve B cell surface. IgE, which is present in serum in very low concentrations, is the major class of immunoglobulin involved in arming mast cells and basophils by binding to these cells via the Fc region. Antigen cross-linking of IgE molecules on basophil and mast cell surfaces results in release of mediators of the immediate hypersensitivity (allergic) response (Table 1-12).

CELLULAR INTERACTIONS IN REGULATION OF NORMAL IMMUNE RESPONSES

The net result of activation of the humoral (B cell) and cellular (T cell) arms of the adaptive immune system by foreign antigen is the elimination of antigen directly by specific effector T cells or in concert with specific antibody. Figure 1-2 is a simplified schematic diagram of the T and B cell responses indicating some of these cellular interactions.

The expression of adaptive immune cell function is the result of a complex series of immunoregulatory events that occur in phases. Both T and B lymphocytes mediate immune functions, and each of these cell types, when given appropriate signals, passes through stages, from activation and induction through proliferation, differentiation, and ultimately effector functions. The effector function expressed may be at the end point of a response, such as secretion of antibody by a differentiated plasma cell, or it might serve a regulatory function that modulates other functions, such as is seen with CD4+ and CD8+ T lymphocytes that modulate both differentiation of B cells and activation of CD8+ cytotoxic T cells.

CD4 helper T cells can be subdivided on the basis of cytokines produced (Fig. 1-2). Activated T_H1-type helper T cells secrete IL-2, IFN-γ, IL-3, TNF-a, GM-CSF, and TNF-β, whereas activated T_H2-type helper T cells secrete IL-3, -4, -5, -6, -10, and -13. T_H1 CD4+ T cells, through elaboration of IFN-γ, have a central role in mediating intracellular killing by a variety of pathogens. T_H1 CD4+ T cells also provide T cell help for generation of cytotoxic T cells and some types of opsonizing antibody, and they generally respond to antigens that lead to delayed hypersensitivity types of immune responses for many intracellular viruses and bacteria (such as HIV or M. tuberculosis). In contrast, T_H2 cells have a primary role in regulatory humoral immunity and isotype switching. T_H2 cells, through production of IL-4 and IL-10, have a regulatory role in limiting proinflammatory responses mediated by T_H1 cells (Fig. 1-2). In addition, T_H2 CD4+ T cells provide help to B cells for specific Ig production and respond to antigens that require high antibody levels for foreign antigen elimination (extracellular encapsulated bacteria such as Streptococcus pneumoniae and certain parasite infections). A new subset of the T_H family has been described, termed T_H17, characterized as cells that secrete cytokines such as IL-17, -22, and -26. T_H17 cells have been shown to play a role in autoimmune inflammatory disorders in addition to defense against extracellular bacteria and fungi, particularly at mucosal surfaces. In summary, the type of T cell response generated in an immune response is determined by the microbe PAMPs presented to the DCs, the TLRs on the DCs that become activated, the types of DCs that are activated, and the cytokines that are produced (Table 1-4). Commonly, myeloid DCs produce IL-12 and activate T_H1 T cell responses that result in IFN-γ and cytotoxic T cell induction, and plasmacytoid DCs produce IFN-α and lead to T_H2 responses that result in IL-4 production and enhanced antibody responses.

As shown in Figs. 1-2 and 1-3, upon activation by DCs, T cell subsets that produce IL-2, IL-3, IFN-γ, and/or IL-4, -5, -6, -10, and -13 are generated and exert positive and negative influences on effector T and B cells. For B cells, trophic effects are mediated by a variety of cytokines, particularly T cell–derived IL-3, -4, -5, and -6, that

act at sequential stages of B cell maturation, resulting in B cell proliferation, differentiation, and ultimately antibody secretion. For cytotoxic T cells, trophic factors include inducer T cell secretion of IL-2, IFN-γ, and IL-12.

An important type of immunomodulatory T cell that controls immune responses is CD4+ and CD8+ T regulatory cells. These cells constitutively express the α chain of the IL-2 receptor (CD25), produce large amounts of IL-10, and can suppress both T and B cell responses. T regulatory cells are induced by immature DCs and play key roles in maintaining tolerance to self-antigens in the periphery. Loss of T regulatory cells is the cause of organ-specific autoimmune disease in mice such as autoimmune thyroiditis, adrenalitis, and oophoritis (see "Immune Tolerance and Autoimmunity" below). T regulatory cells also play key roles in controlling the magnitude and duration of immune responses to microbes. Normally, after the initial immune response to a microbe has eliminated the invader, T regulatory cells are activated to suppress the antimicrobe response and prevent host injury. Some microbes have adapted to induce T regulatory cell activation at the site of infection to promote parasite infection and survival. In Leishmania infection, the parasite locally induces T regulatory cell accumulation at skin infection sites that dampens anti-Leishmania T cell responses and prevents elimination of the parasite. It is thought that many chronic infections such as by M. tuberculosis are associated with abnormal T regulatory cell activation that prevents elimination of the microbe.

Although B cells recognize native antigen via B cell–surface Ig receptors, B cells require T cell help to produce high-affinity antibody of multiple isotypes that are the most effective in eliminating foreign antigen. This T cell dependence likely functions in the regulation of B cell responses and in protection against excessive autoantibody production. T cell–B cell interactions that lead to high-affinity antibody production require (1) processing of native antigen by B cells and expression of peptide fragments on the B cell surface for presentation to T_H cells, (2) the ligation of B cells by both the TCR complex and the CD40 ligand, (3) induction of the process termed antibody isotype switching in antigen-specific B cell clones, and (4) induction of the process of affinity maturation of antibody in the germinal centers of B cell follicles of lymph node and spleen.

Naïve B cells express cell-surface IgD and IgM, and initial contact of naïve B cells with antigen is via binding of native antigen to B cell–surface IgM. T cell cytokines, released following T_H2 cell contact with B cells or by a "bystander" effect, induce changes in Ig gene conformationthat promote recombination of Ig genes. These events then result in the "switching" of expression of heavy chain exons in a triggered B cell, leading to the secretion of IgG, IgA, or, in some cases, IgE antibody with the same V region antigen specificity as the original IgM antibody, for response to a wide variety of extracellular bacteria, protozoa, and helminths. CD40 ligand expression by activated T cells is critical for induction of B cell antibody isotype switching and for B cell responsiveness to cytokines. Patients with mutations in T cell CD40 ligand have B cells that are unable to undergo isotype switching, resulting in lack of memory B cell generation and the immunodeficiency syndrome of X-linked hyper-IgM syndrome.

IMMUNE TOLERANCE AND AUTOIMMUNITY

Immune tolerance is defined as the absence of activation of pathogenic autoreactivity. Autoimmune diseases are syndromes caused by the activation of T or B cells or both, with no evidence of other causes such as infections or malignancies. Once thought to be mutually exclusive, immune tolerance and autoimmunity are now both recognized to be present normally in health; when abnormal, they represent extremes from the normal state. For example, it is now known that low levels of autoreactivity of T and B cells with self-antigens in the periphery are critical to their survival. Similarly, low levels of autoreactivity and thymocyte recognition of self-antigens in the thymus are the mechanisms whereby (1) normal T cells are positively selected to survive and leave the thymus to respond to foreign microbes in the periphery and (2) T cells highly reactive to self-antigens are negatively selected and die to prevent overly self-reactive T cells from getting into the periphery (central tolerance). However, not all self-antigens are expressed in the thymus to delete highly self-reactive T cells, and there are mechanisms for peripheral tolerance induction of T cells as well. Unlike the presentation of microbial antigens by mature DCs, the presentation of self-antigens by immature DCs neither activates nor matures the DCs to express high levels of co-stimulatory molecules such as B7-1 (CD80) or B7-2 (CD86). When peripheral T cells are stimulated by DCs expressing self-antigens in the context of HLA molecules, sufficient stimulation of T cells occurs to keep them alive, but otherwise they remain anergic, or nonresponsive, until they contact a DC with high levels of co-stimulatory molecules expressing microbial antigens. In the latter setting, normal T cells then become activated to respond to the microbe. If B cells have high-self-reactivity BCRs, they normally undergo either deletion in the bone marrow or receptor editing to express a less autoreactive receptor. Although many autoimmune diseases are characterized by abnormal or pathogenic autoantibody production **(Table 1-13)**, most autoimmune diseases are caused by a combination of excess T and B cell reactivity.

Multiple factors contribute to the genesis of clinical autoimmune disease syndromes, including genetic susceptibility (Table 1-13), environmental immune stimulants such as drugs (e.g., procainamide and phenytoin

TABLE 1-13

RECOMBINANT OR PURIFIED AUTOANTIGENS RECOGNIZED BY AUTOANTIBODIES ASSOCIATED WITH HUMAN AUTOIMMUNE DISORDERS

AUTOANTIGEN	AUTOIMMUNE DISEASES
Cell- or Organ-Specific Autoimmunity	
Acetylcholine receptor	Myasthenia gravis
Actin	Chronic active hepatitis, primary biliary cirrhosis
Adenine nucleotide translator (ANT)	Dilated cardiomyopathy, myocarditis
β-Adrenoreceptor	Dilated cardiomyopathy
Aromatic l-amino acid decarboxylase	Autoimmune polyendocrine syndrome type 1 (APS-1)
Asialoglycoprotein receptor	Autoimmune hepatitis
Bactericidal/permeability-increasing protein (Bpi)	Cystic fibrosis vasculitides
Calcium-sensing receptor	Acquired hypoparathyroidism
Cholesterol side-chain cleavage enzyme (CYPlla)	Autoimmune polyglandular syndrome-1
Collagen type IV-α3-chain	Goodpasture's syndrome
Cytochrome P450 2D6 (CYP2D6)	Autoimmune hepatitis
Desmin	Crohn's disease, coronary artery disease
Desmoglein 1	Pemphigus foliaceus
Desmoglein 3	Pemphigus vulgaris
F-actin	Autoimmune hepatitis
GM gangliosides	Guillain-Barré syndrome
Glutamate decarboxylase (GAD65)	Type 1 diabetes, stiff-person syndrome
Glutamate receptor (GLUR)	Rasmussen encephalitis
H/KATPase	Autoimmune gastritis
17-α-Hydroxylase (CYP17)	Autoimmune polyglandular syndrome-1
21-Hydroxylase (CYP21)	Addison's disease
IA-2 (ICA512)	Type 1 diabetes
Insulin	Type 1 diabetes, insulin hypoglycemic syndrome (Hirata's disease)
Insulin receptor	Type B insulin resistance, acanthosis, systemic lupus erythematosus (SLE)
Intrinsic factor type 1	Pernicious anemia
Leukocyte function-associated antigen (LFA-1)	Treatment-resistant Lyme arthritis
Myelin-associated glycoprotein (MAG)	Polyneuropathy
Myelin-basic protein	Multiple sclerosis, demyelinating diseases
Myelin oligodendrocyte glycoprotein (MOG)	Multiple sclerosis
Myosin	Rheumatic fever
p-80-Collin	Atopic dermatitis
Pyruvate dehydrogenase complex-E2 (PDC-E2)	Primary biliary cirrhosis
Sodium iodide symporter (NIS)	Graves' disease, autoimmune hypothyroidism
SOX-10	Vitiligo
Thyroid and eye muscle shared protein	Thyroid-associated ophthalmopathy
Thyroglobulin	Autoimmune thyroiditis
Thyroid peroxidase	Autoimmune Hashimoto's thyroiditis
Thyrotropin receptor	Graves' disease
Tissue transglutaminase	Celiac disease
Transcription coactivator p75	Atopic dermatitis
Tryptophan hydroxylase	Autoimmune polyglandular syndrome-1
Tyrosinase	Vitiligo, metastatic melanoma
Tyrosine hydroxylase	Autoimmune polyglandular syndrome-1
Systemic Autoimmunity	
ACTH	ACTH deficiency
Aminoacyl-tRNA histidyl synthetase	Myositis, dermatomyositis
Aminoacyl-tRNA synthetase (several)	Polymyositis, dermatomyositis
Cardiolipin	Systemic lupus erythematosus, antiphospholipid syndrome
Carbonic anhydrase II	Systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis
Histone H2A-H2B-DNA	Systemic lupus erythematosus
IgE receptor	Chronic idiopathic urticaria
Keratin	Rheumatoid arthritis
Ku-DNA-protein kinase	Systemic lupus erythematosus
Ku-nucleoprotein La phosphoprotein (La 55-B)	Connective tissue syndrome Sjögren's syndrome

(continued)

TABLE 1-13

RECOMBINANT OR PURIFIED AUTOANTIGENS RECOGNIZED BY AUTOANTIBODIES ASSOCIATED WITH HUMAN AUTOIMMUNE DISORDERS (CONTINUED)

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES
Systemic Autoimmunity			
Collagen (multiple types)	Rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis	Myeloperoxidase	Necrotizing and crescentic glomerulonephritis (NCGN), systemic vasculitis
Centromere-associated proteins	Systemic sclerosis	Proteinase 3 (PR3)	Granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
DNA-dependent nucleoside-stimulated ATPase	Dermatomyositis	RNA polymerase I–III (RNP)	Systemic sclerosis, systemic lupus erythematosus
Fibrillarin	Systemic sclerosis	Signal recognition protein (SRP54)	Polymyositis
Fibronectin	Systemic lupus erythematosus, rheumatoid arthritis, morphea	Topoisomerase-1 (Scl-70)	Scleroderma, Raynaud's syndrome
Glucose-6-phosphate isomerase	Rheumatoid arthritis	Tublin	Chronic liver disease, visceral leishmaniasis
β2-Glycoprotein I (B2-GPI)	Primary antiphospholipid syndrome	Vimentin	Systemic autoimmune disease
Golgin (95, 97, 160, 180) Heat shock protein	Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis Various immune-related disorders		
Hemidesmosomal protein 180	Bullous pemphigoid, herpes gestationis, cicatricial pemphigoid		
Plasma Protein and Cytokine Autoimmunity			
C1 inhibitor	Autoimmune C1 deficiency	Glycoprotein IIb/IIIg and Ib/IX	Autoimmune thrombocytopenia purpura
C1q	Systemic lupus erythematosus, membrane proliferative glomerulonephritis (MPGN)	IgA	Immunodeficiency associated with systemic lupus erythematosus, pernicious anemia, thyroiditis, Sjögren's syndrome, and chronic active hepatitis
Cytokines (IL-1α, IL-1β, IL-6, IL-10, LIF)	Rheumatoid arthritis, systemic sclerosis, healthy subjects	Oxidized LDL (OxLDL)	Atherosclerosis
Factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, thrombin vWF	Prolonged coagulation time		
Cancer and Paraneoplastic Autoimmunity			
Amphiphysin	Neuropathy, small-cell lung cancer	p62 (IGF-II mRNA-binding protein)	Hepatocellular carcinoma (China)
Cyclin B1	Hepatocellular carcinoma	Recoverin	Cancer-associated retinopathy
DNA topoisomerase II	Liver cancer	Ri protein	Paraneoplastic opsoclonus myoclonus ataxia
Desmoplakin	Paraneoplastic pemphigus	βIV spectrin	Lower motor neuron syndrome
Gephyrin	Paraneoplastic stiff-person syndrome	Synaptotagmin	Lambert-Eaton myasthenic syndrome
Hu proteins	Paraneoplastic encephalomyelitis	Voltage-gated calcium channels	Lambert-Eaton myasthenic syndrome
Neuronal nicotinic acetylcholine receptor	Subacute autonomic neuropathy, cancer	Yo protein	Paraneoplastic cerebellar degeneration
p53	Cancer, systemic lupus erythematosus		

Source: From A Lernmark et al: J Clin Invest 108:1091, 2001; with permission.

[Dilantin] with drug-induced systemic lupus erythematosus), infectious agent triggers (such as Epstein-Barr virus and autoantibody production against red blood cells and platelets), and loss of T regulatory cells (leading to thyroiditis, adrenalitis, and oophoritis).

Immunity at mucosal surfaces

Mucosa covering the respiratory, digestive, and urogenital tracts; the eye conjunctiva; the inner ear; and the ducts of all exocrine glands contain cells of the innate and adaptive mucosal immune system that protect these surfaces against pathogens. In the healthy adult, mucosa-associated lymphoid tissue (MALT) contains 80% of all immune cells within the body and constitutes the largest mammalian lymphoid organ system.

MALT has three main functions: (1) to protect the mucous membranes from invasive pathogens; (2) to prevent uptake of foreign antigens from food, commensal organisms, and airborne pathogens and particulate matter; and (3) to prevent pathologic immune responses from foreign antigens if they do cross the mucosal barriers of the body **(Fig. 1-9)**.

MALT is a compartmentalized system of immune cells that functions independently from systemic immune organs. Whereas the systemic immune organs are essentially sterile under normal conditions and respond vigorously to pathogens, MALT immune cells are continuously bathed in foreign proteins and commensal bacteria, and they must select those pathogenic antigens that must be eliminated. MALT contains anatomically defined foci of immune cells in the intestine, tonsil, appendix, and peribronchial areas that are inductive sites for mucosal immune responses. From these sites, immune T and B cells migrate to effector sites in mucosal parenchyma and exocrine glands where mucosal immune cells eliminate pathogen-infected cells. In addition to mucosal immune responses, all mucosal sites have strong mechanical and chemical barriers and cleansing functions to repel pathogens.

Key components of MALT include specialized epithelial cells called "membrane" or "M" cells that take up antigens and deliver them to DCs or other APCs. Effector cells in MALT include B cells producing antipathogen neutralizing antibodies of secretory IgA as well as IgG isotype, T cells producing similar cytokines as in systemic immune system response, and T helper and cytotoxic T cells that respond to pathogen-infected cells.

Secretory IgA is produced in amounts of >50 mg/kg of body weight per 24 h and functions to inhibit

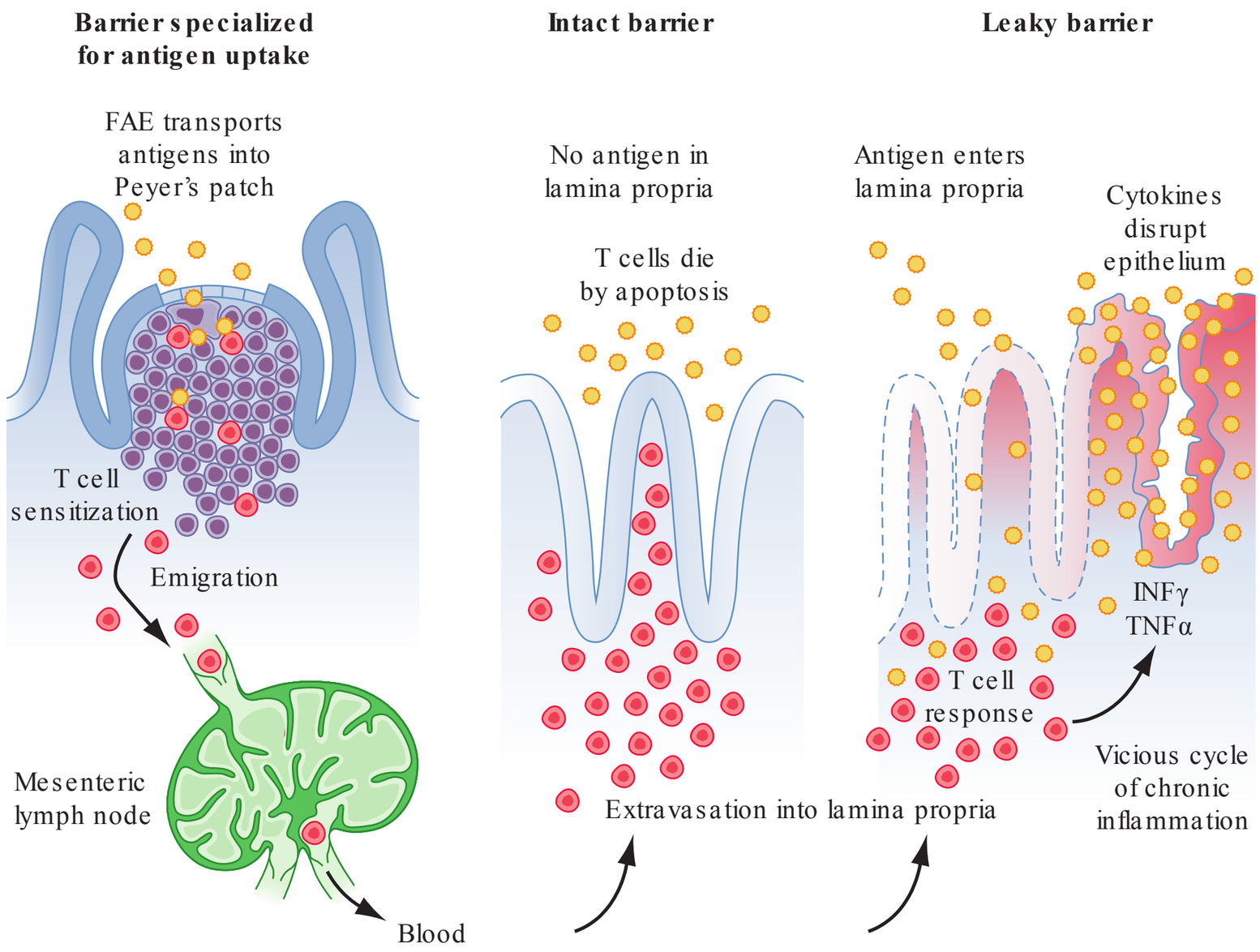


FIGURE 1-9

Increased epithelial permeability may be important in the development of chronic gut T cell–mediated inflammation. CD4 T cells activated by gut antigens in Peyer's patches migrate to the lamina propria (LP). In healthy individuals, these cells die by apoptosis. Increased epithelial permeability may allow sufficient antigen to enter the LP to trigger T cell activation, breaking tolerance mediated by immunosuppressive cytokines and perhaps T regulatory cells. Proinflammatory cytokines then further increase epithelial permeability, setting up a vicious cycle of chronic inflammation. (From TT MacDonald et al: Science 307:1920, 2005; with permission.)

bacterial adhesion, inhibit macromolecule absorption in the gut, neutralize viruses, and enhance antigen elimination in tissue through binding to IgA and receptor-mediated transport of immune complexes through epithelial cells.

Recent studies have demonstrated the importance of commensal gut and other mucosal bacteria to the health of the human immune system. Normal commensal flora induces anti-inflammatory events in the gut and protects epithelial cells from pathogens through TLRs and other PRR signaling. When the gut is depleted of normal commensal flora, the immune system becomes abnormal, with loss of T_H1 T cell function. Restoration of the normal gut flora can reestablish the balance in T helper cell ratios characteristic of the normal immune system. When the gut barrier is intact, either antigens do not transverse the gut epithelium or, when pathogens are present, a self-limited, protective MALT immune response eliminates the pathogen (Fig. 1-9). However, when the gut barrier breaks down, immune responses to commensal flora antigens can cause inflammatory bowel diseases such as Crohn's disease and, perhaps, ulcerative colitis (Fig. 1-9). Uncontrolled MALT immune responses to food antigens, such as gluten, can cause celiac disease.

THE CELLULAR AND MOLECULAR CONTROL OF PROGRAMMED CELL DEATH

The process of apoptosis (programmed cell death) plays a crucial role in regulating normal immune responses to antigen. In general, a wide variety of stimuli trigger one of several apoptotic pathways to eliminate microbe-infected cells, eliminate cells with damaged DNA, or eliminate activated immune cells that are no longer needed **(Fig. 1-10)**. The largest known family of "death receptors" is the TNF receptor (TNF-R) family (TNF-R1, TNF-R2, Fas [CD95], death receptor 3 [DR3], death receptor 4 [DR4; TNF-related apoptosis-including ligand receptor 1, or TRAIL-R1], and death receptor 5 [DR5, TRAIL-R2]); their ligands are all in the TNF-α family. Binding of ligands to these death receptors leads to a signaling cascade that involves activation of the caspase family of molecules that leads to DNA cleavage and cell death. Two other pathways of programmed cell death involve nuclear p53 in the elimination of cells with abnormal DNA and mitochondrial cytochrome c to induce cell death in damaged cells (Fig. 1-10). A number of human diseases have now been described that result from, or are associated with, mutated apoptosis genes **(Table 1-14)**. These include mutations in the Fas and Fas ligand genes in autoimmune and lymphoproliferation syndromes, and multiple associations of mutations in genes in the apoptotic pathway with malignant syndromes.

MECHANISMS OF IMMUNE-MEDIATED DAMAGE TO MICROBES OR HOST TISSUES

Several responses by the host innate and adaptive immune systems to foreign microbes culminate in rapid and efficient elimination of microbes. In these scenarios, the classic weapons of the adaptive immune system (T cells, B cells) interface with cells (macrophages, DCs, NK cells, neutrophils, eosinophils, basophils) and soluble products (microbial peptides, pentraxins, complement and coagulation systems) of the innate immune system.

There are five general phases of host defenses: (1) migration of leukocytes to sites of antigen localization; (2) antigen-nonspecific recognition of pathogens by macrophages and other cells and systems of the innate immune system; (3) specific recognition of foreign antigens mediated by T and B lymphocytes; (4) amplification of the inflammatory response with recruitment of specific and nonspecific effector cells by complement components, cytokines, kinins, arachidonic acid metabolites, and mast cell–basophil products; and (5) macrophage, neutrophil, and lymphocyte participation in destruction of antigen with ultimate removal of antigen particles by phagocytosis (by macrophages or neutrophils) or by direct cytotoxic mechanisms (involving macrophages, neutrophils, DCs, and lymphocytes). Under normal circumstances, orderly progression of host defenses through these phases results in a well-controlled immune and inflammatory response that protects the host from the offending antigen. However, dysfunction of any of the host defense systems can damage host tissue and produce clinical disease. Furthermore, for certain pathogens or antigens, the normal immune response itself might contribute substantially to the tissue damage. For example, the immune and inflammatory response in the brain to certain pathogens such as M. tuberculosis may be responsible for much of the morbidity rate of this disease in that organ system. In addition, the morbidity rate associated with certain pneumonias such as that caused by Pneumocystis jiroveci may be associated more with inflammatory infiltrates than with the tissue-destructive effects of the microorganism itself.

Molecular basis of lymphocyte–endothelial cell interactions

The control of lymphocyte circulatory patterns between the bloodstream and peripheral lymphoid organs operates at the level of lymphocyte–endothelial cell interactions to control the specificity of lymphocyte subset entry into organs. Similarly, lymphocyte–endothelial cell interactions regulate the entry of lymphocytes into inflamed tissue. Adhesion molecule expression on lymphocytes and endothelial cells regulates the

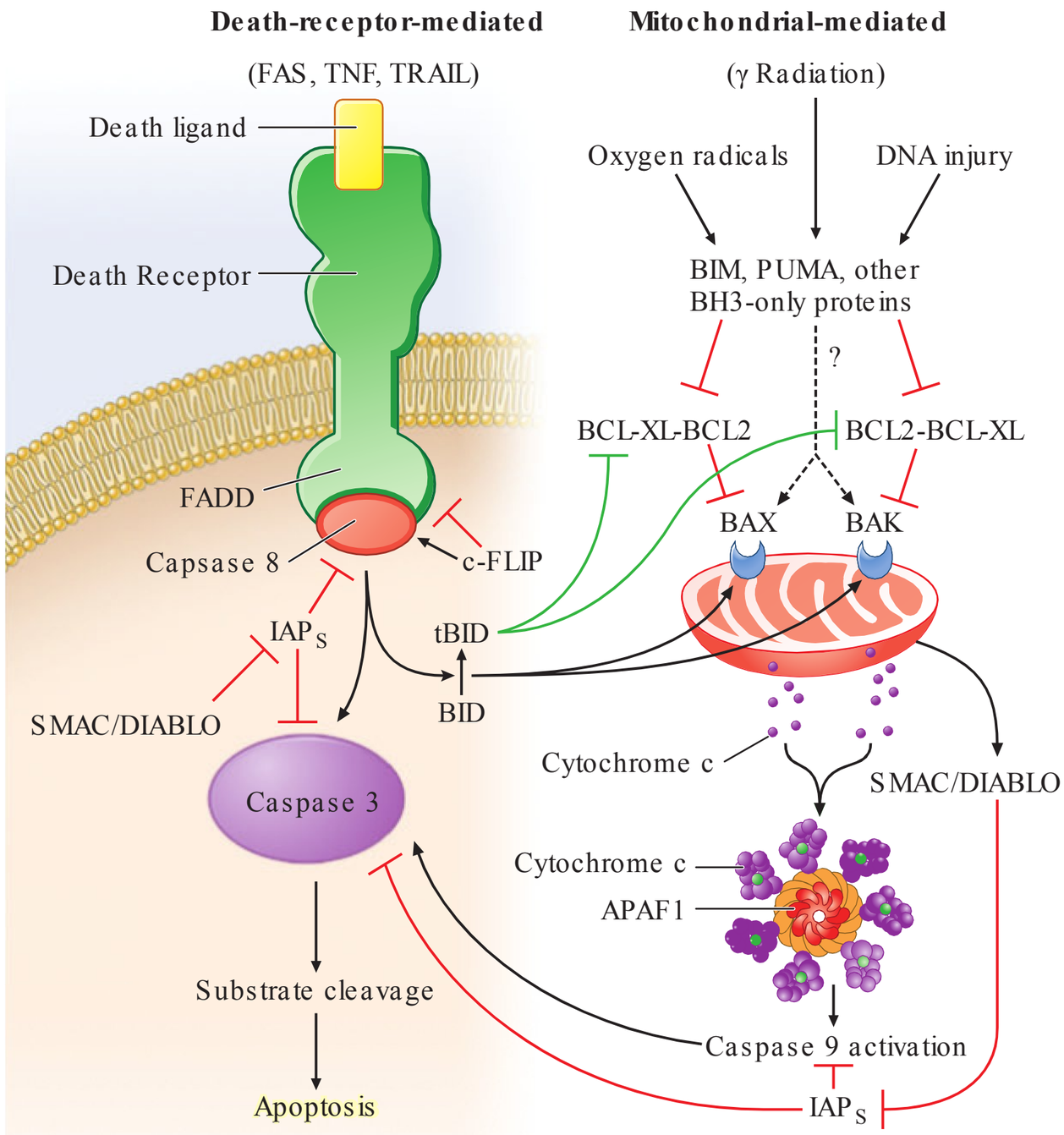


FIGURE 1-10

Pathways of cellular apoptosis. There are two major pathways of apoptosis: the death-receptor pathway, which is mediated by activation of death receptors, and the BCL2-regulated mitochondrial pathway, which is mediated by noxious stimuli that ultimately lead to mitochondrial injury. Ligation of death receptors recruits the adaptor protein FAS-associated death domain (FADD). FADD in turn recruits caspase 8, which ultimately activates caspase 3, the key "executioner" caspase. Cellular FLICE-inhibitory protein (c-FLIP) can either inhibit or potentiate binding of FADD and caspase 8, depending on its concentration. In the intrinsic pathway, proapoptotic BH3 proteins are activated by noxious stimuli, which interact with and inhibit antiapoptotic BCL2 or BCL-XL. Thus, BAX and BAK are free to induce mitochondrial permeabilization with release of cytochrome c, which ultimately results in the activation of caspase 9 through the apoptosome. Caspase 9 then activates caspase 3. SMAC/DIABLO is also released after mitochondrial permeabilization and acts to block the action of inhibitors of apoptosis protein (IAPs), which inhibit caspase activation. There is potential cross-talk between the two pathways, which is mediated by the truncated form of BID (tBID) that is produced by caspase 8–mediated BID cleavage; tBID acts to inhibit the BCL2-BCL-XL pathway and to activate BAX and BAK. There is debate (indicated by the question mark) as to whether proapoptotic BH3 molecules (e.g., BIM and PUMA) act directly on BAX and BAK to induce mitochondrial permeability or whether they act only on BCL2-BCL-XL. APAF1, apoptotic protease-activating factor 1; BH3, BCL homologue; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand. (From RS Hotchkiss et al: N Engl J Med 361:1570, 2009; with permission.)

retention and subsequent egress of lymphocytes within tissue sites of antigenic stimulation, delaying cell exit from tissue and preventing reentry into the circulating lymphocyte pool **(Fig. 1-11)**. All types of lymphocyte migration begin with lymphocyte attachment to specialized regions of vessels, termed high endothelial venules (HEVs). An important concept is that adhesion molecules do not generally bind their ligand until a conformational change (ligand activation) occurs in the adhesion molecule that allows ligand binding. Induction of a conformation-dependent determinant on an adhesion molecule can be accomplished by cytokines or via ligation of other adhesion molecules on the cell.

The first stage of lymphocyte–endothelial cell interactions, attachment and rolling, occurs when lymphocytes leave the stream of flowing blood cells in a postcapillary venule and roll along venule endothelial cells (Fig. 1-11). Lymphocyte rolling is mediated by the l-selectin molecule (LECAM-1, LAM-1, CD62L) and

TABLE 1-14

IMMUNE SYSTEM MOLECULE DEFECTS IN ANIMALS OR HUMANS THAT CAUSE AUTOIMMUNE OR MALIGNANT SYNDROMES

PROTEIN	DEFECT	DISEASE OR SYNDROME	OBSERVATION IN ANIMAL MODELS OR HUMANS
Cytokines and Signaling Proteins			
Tumor necrosis factor (TNF) α	Overexpression	Inflammatory bowel disease (IBD), arthritis, vasculitis	Mice
TNF-α	Underexpression	Systemic lupus erythematosus (SLE)	Mice
Interleukin (IL)-1-receptor antagonist	Underexpression	Arthritis	Mice
IL-2	Overexpression	IBD	Mice
IL-7	Overexpression	IBD	Mice
IL-10	Overexpression	IBD	Mice
IL-2 receptor	Overexpression	IBD	Mice
IL-10 receptor	Overexpression	IBD	Mice
IL-3	Overexpression	Demyelinating syndrome	Mice
Interferon-δ	Overexpression in skin	SLE	Mice
STAT-3	Underexpression	IBD	Mice
STAT-4	Overexpression	IBD	Mice
Transforming growth factor (TGF) β	Underexpression	Systemic wasting syndrome and IBD	Mice
TGF-β receptor in T cells	Underexpression	SLE	Mice
Programmed death (CD279, PD-1)	Underexpression	SLE-like syndrome	Mice
Cytotoxic T lymphocyte, antigen-4 (CTLA-4)	Underexpression	Systemic lymphoproliferative disease	Mice
IL-10	Underexpression	IBD (mouse), type 1 diabetes, thyroid disease, primary (human)	Mice and humans
Major Histocompatibility Locus Molecules[a]			
HLA-B27	Allele expression or overexpression	Inflammatory bowel disease	Rats and humans
Complement deficiency of C1, 2, 3 or 4	Underexpression		Humans
LIGHT (TNF superfamily 14)	Overexpression	Systemic lymphoproliferative (mouse) and autoimmunity	Mice
HLA class II DQB10301, DQB10302	Allele expression	Juvenile-onset diabetes	Humans
HLA class II DQB10401, DQB10402	Allele expression	Rheumatoid arthritis	Humans
HLA class I B27	Allele expression	Ankylosing spondylitis, IBD	Rats and humans
Apoptosis Proteins			
TNF receptor 1 (TNF-R1)	Underexpression	Familial periodic fever syndrome	Humans
Fas (CD95; Apo-1)	Underexpression	Autoimmune lymphoproliferative syndrome type 1 (ALPS 1); malignant lymphoma; bladder cancer	Humans
Fas ligand	Underexpression	SLE (only one case identified)	Humans

(continued)

TABLE 1-14

IMMUNE SYSTEM MOLECULE DEFECTS IN ANIMALS OR HUMANS THAT CAUSE AUTOIMMUNE OR MALIGNANT SYNDROMES (CONTINUED)

PROTEIN	DEFECT	DISEASE OR SYNDROME	OBSERVATION IN ANIMAL MODELS OR HUMANS
Perforin	Underexpression	Familial hemophagocytic lymphohistiocytosis (FHL)	Humans
Caspase 10	Underexpression	Autoimmune lymphoproliferative syndrome type II (ALPS II)	Humans
bcl-10	Underexpression	Non-Hodgkin's lymphoma	Humans
P53	Underexpression	Various malignant neoplasms	Humans
Bax	Underexpression	Colon cancer; hematopoietic malignancies	Humans
bcl-2	Underexpression	Non-Hodgkin's lymphoma	Humans
c-IAP2	Underexpression	Low-grade MALT lymphoma	Humans
NAIP1	Underexpression	Spinal muscular atrophy	Humans

[a]Many autoimmune diseases are associated with a myriad of major histocompatibility complex gene allele (HLA) types. They are presented here as examples.

Abbreviation: MALT, mucosa-associated lymphoid tissue.

Source: Adapted from L Mullauer: Mutat Res 488:211, 2001 and A Davidson, B Diamond: N Engl J Med 345:340, 2001.

slows cell transit time through venules, allowing time for activation of adherent cells.

The second stage of lymphocyte–endothelial cell interactions, *f*irm adhesion with activation-dependent stable arrest, requires stimulation of lymphocytes by chemoattractants or by endothelial cell–derived cytokines. Cytokines thought to participate in adherent cell activation include members of the IL-8 family, platelet-activation factor, leukotriene B_4, and C5a. In addition, HEVs express chemokines, SLC (CCL21) and ELC (CCL19), which participate in this process. Following activation by chemoattractants, lymphocytes shed l-selectin from the cell surface and upregulate cell CD11b/18 (MAC-1) or CD11a/18 (LFA-1) molecules, resulting in firm attachment of lymphocytes to HEVs.

Lymphocyte homing to peripheral lymph nodes involves adhesion of l-selectin to glycoprotein HEV ligands collectively referred to as peripheral node addressin (PNAd), whereas homing of lymphocytes to intestine Peyer's patches primarily involves adhesion of the a4β7 integrin to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the Peyer's patch HEVs. However, for migration to mucosal Peyer's patch lymphoid aggregates, naïve lymphocytes primarily use l-selectin, whereas memory lymphocytes use a4β7 integrin. a4β1 integrin (CD49d/CD29, VLA-4)–VCAM-1 interactions are important in the initial interaction of memory lymphocytes with HEVs of multiple organs in sites of inflammation **(Table 1-15)**.

The third stage of leukocyte emigration in HEVs is sticking and arrest. Sticking of the lymphocyte to endothelial cells and arrest at the site of sticking are mediated predominantly by ligation of a1β2 integrin LFA-1 to the integrin ligand ICAM-1 on HEVs. Whereas the first three stages of lymphocyte attachment to HEVs take only a few seconds, the fourth stage of lymphocyte emigration, transendothelial migration, takes ~10 min. Although the molecular mechanisms that control lymphocyte transendothelial migration are not fully characterized, the HEV CD44 molecule and molecules of the HEV glycocalyx (extracellular matrix) are thought to play important regulatory roles in this process (Fig. 1-11). Finally, expression of matrix metalloproteases capable of digesting the subendothelial basement membrane, rich in nonfibrillar collagen, appears to be required for the penetration of lymphoid cells into the extravascular sites.

Abnormal induction of HEV formation and use of the molecules discussed above have been implicated in the induction and maintenance of inflammation in a number of chronic inflammatory diseases. In animal models of type 1 diabetes mellitus, MAdCAM-1 and GlyCAM-1 have been shown to be highly expressed on HEVs in inflamed pancreatic islets, and treatment of these animals with inhibitors of l-selectin and a4 integrin function blocked the development of type 1 diabetes mellitus. A similar role for abnormal induction of the adhesion molecules of lymphocyte emigration has been suggested in rheumatoid arthritis, Hashimoto's thyroiditis, Graves' disease, multiple sclerosis, Crohn's disease, and ulcerative colitis.

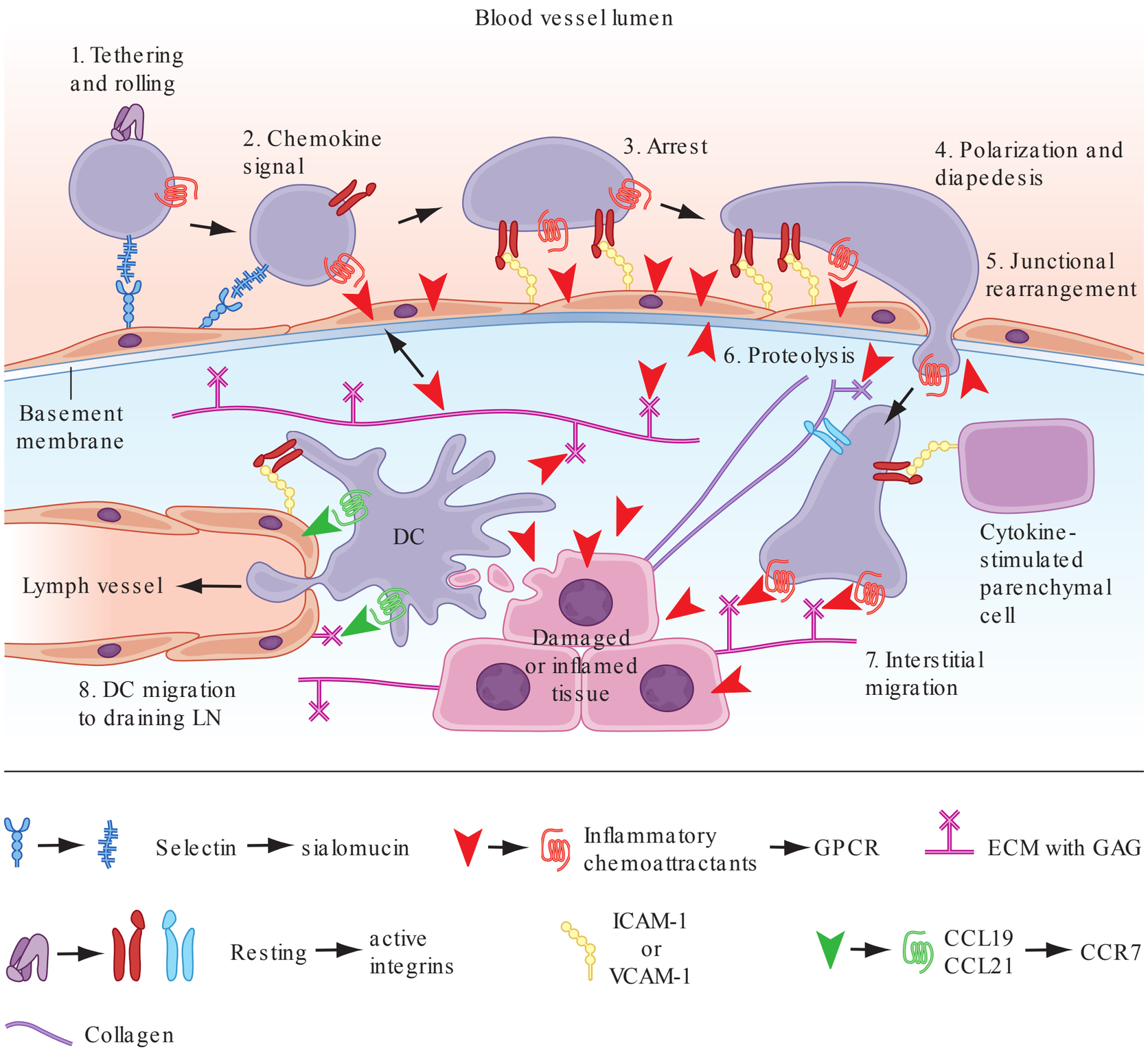


FIGURE 1-11

Key migration steps of immune cells at sites of inflammation. Inflammation due to tissue damage or infection induces the release of cytokines (not shown) and inflammatory chemoattractants (red arrowheads) from distressed stromal cells and "professional" sentinels, such as mast cells and macrophages (not shown). The inflammatory signals induce upregulation of endothelial selectins and immunoglobulin "superfamily" members, particularly ICAM-1 and/or VCAM-1. Chemoattractants, particularly chemokines, are produced by or translocated across venular endothelial cells (red arrow) and are displayed in the lumen to rolling leukocytes. Those leukocytes that express the appropriate set of trafficking molecules undergo a multistep adhesion cascade (steps 1–3) and then polarize and move by diapedesis across the venular wall (steps 4 and 5). Diapedesis involves transient disassembly of endothelial junctions and penetration through the underlying basement membrane (step 6). Once in the extravascular (interstitial) space, the migrating cell uses different integrins to gain "footholds" on collagen fibers and other ECM molecules, such as laminin and fibronectin, and on inflammation-induced ICAM-1 on the surface of parenchymal cells (step 7). The migrating cell receives guidance cues from distinct sets of chemoattractants, particularly chemokines, which may be immobilized on glycosaminoglycans (GAG) that "decorate" many ECM molecules and stromal cells. Inflammatory signals also induce tissue dendritic cells (DCs) to undergo maturation. Once DCs process material from damaged tissues and invading pathogens, they upregulate CCR7, which allows them to enter draining lymph vessels that express the CCR7 ligand CCL21 (and CCL19). In lymph nodes (LNs), these antigen-loaded mature DCs activate naïve T cells and expand pools of effector lymphocytes, which enter the blood and migrate back to the site of inflammation. T cells in tissue also use this CCR7-dependent route to migrate from peripheral sites to draining lymph nodes through afferent lymphatics. (Adapted from AD Luster et al: Nat Immunol 6:1182, 2005; with permission from Macmillan Publishers Ltd. Copyright 2005.)

Immune-complex formation

Clearance of antigen by immune-complex formation between antigen, complement, and antibody is a highly effective mechanism of host defense. However, depending on the level of immune complexes formed and their physicochemical properties, immune complexes may or may not result in host and foreign cell damage. After antigen exposure, certain types of soluble antigen-antibody complexes freely circulate and, if not cleared by the reticuloendothelial system, can be deposited in blood vessel walls and in other tissues such as renal glomeruli and cause vasculitis or glomerulonephritis

TABLE 1-15

TRAFFICKING MOLECULES INVOLVED IN INFLAMMATORY DISEASE PROCESSES

		PROPOSED LEUKOCYTE RECEPTORS FOR ENDOTHELIAL TRAFFIC SIGNALS		
DISEASE	KEY EFFECTOR CELL	L-SELECTIN, LIGAND	GPCR	INTEGRIN[a]
Acute Inflammation				
Myocardial infarction	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Stroke	Neutrophil	l-Selectin, PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Ischemia-reperfusion	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
T_H1 Inflammation				
Atherosclerosis	Monocyte	PSGL-1	CCR1, CCR2, BLT1, CXCR2, CX3CR1	VLA-4
	T_H1	PSGL-1	CXCR3, CCR5	VLA-4
Multiple sclerosis	T_H1	PSGL-1 (?)	CXCR3, CXCR6	VLA-4, LFA-1
	Monocyte	PSGL-1 (?)	CCR2, CCR1	VLA-4, LFA-1
Rheumatoid arthritis	Monocyte	PSGL-1	CCR1, CCR2	VLA-1, VLA-2, VLA-4, LFA-1
	T_H1	PSGL-1	CXCR3, CXCR6	VLA-1, VLA-2, VLA-4, LFA-1
	Neutrophil	l-Selectin, PSGL-1	CXCR2, BLT1	LFA-1[b]
Psoriasis	Skin-homing T_H1	CLA	CCR4, CCR10, CXCR3	VLA-4[c], LFA-1
Crohn's disease	Gut-homing T_H1	PSGL-1	CCR9, CXCR3	α4, β7, LFA-1
Type 1 diabetes	T_H1	PSGL-1 (?)	CCR4, CCR5	VLA-4, LFA-1
	CD8	l-Selectin (?), PSGL-1 (?)	CXCR3	VLA-4, LFA-1
Allograft rejection	CD8	PSGL-1	CXCR3, CX3CR1, BLT1	VLA-4, LFA-1
	B cell	l-Selectin, PSGL-1	CXCR5, CXCR4	VLA-4, LFA-1
Hepatitis	CD8	PSGL-1	CXCR3, CCR5, CXCR6	VLA-4
Lupus	T_H1	None	CXCR6	VLA-4[d]
	Plasmacytoid DC	l-Selectin, CLA	CCR7, CXCR3, ChemR23	LFA-1, Mac-1
	B cell	CLA (?)	CXCR5, CXCR4	LFA-1
T_H2 Inflammation				
Asthma	T_H2	PSGL-1	CCR4, CCR8, BLT1	LFA-1
	Eosinophil	PSGL-1	CCR3, PAFR, BLT1	VLA-4, LFA-1
	Mast cells	PSGL-1	CCR2, CCR3, BLT1	VLA-4, LFA-1
Atopic dermatitis	Skin-homing T_H2	CLA	CCR4, CCR10	VLA-4, LFA-1

[a]Various β_1 integrins have been linked in different ways in basal lamina and interstitial migration of distinct cell types and inflammatory settings.
[b]In some settings, Mac-1 has been linked to transmigration.
[c]CD44 can act in concert with VLA-4 in particular models of leukocyte arrest.
[d]T_H2 cells require VAP-1 to traffic to inflamed liver.
Source: From AD Luster et al: Nat Immunol 6:1182, 2005; with permission from Macmillan Publishers Ltd. Copyright 2005.

syndromes **(Chap. 11)**. Deficiencies of early complement components are associated with inefficient clearance of immune complexes and immune complex mediated tissue damage in autoimmune syndromes, whereas deficiencies of the later complement components are associated with susceptibility to recurrent Neisseria infections **(Table 1-16)**.

Immediate-type hypersensitivity

Helper T cells that drive antiallergen IgE responses are usually T_H2-type inducer T cells that secrete IL-4, IL-5, IL-6, and IL-10. Mast cells and basophils have high-affinity receptors for the Fc portion of IgE (FcRI), and cell-bound antiallergen IgE effectively "arms" basophils

TABLE 1-16

COMPLEMENT DEFICIENCIES AND ASSOCIATED DISEASES

COMPONENT	ASSOCIATED DISEASES
Classic Pathway	
Clq, Clr, Cls, C4	Immune-complex syndromes,[a] pyogenic infections
C2	Immune-complex syndromes,[a] few with pyogenic infections
C1 inhibitor	Rare immune-complex disease, few with pyogenic infections
C3 and Alternative Pathway C3	
C3	Immune-complex syndromes,[a] pyogenic infections
D	Pyogenic infections
Properdin	Neisseria infections
I	Pyogenic infections
H	Hemolytic-uremic syndrome
Membrane Attack Complex	
C5, C6, C7, C8	Recurrent Neisseria infections, immune-complex disease
C9	Rare Neisseria infections

[a]Immune-complex syndromes include systemic lupus erythematosus (SLE) and SLE-like syndromes, glomerulonephritis, and vasculitis syndromes.

Source: After JA Schifferli, DK Peters: Lancet 322:957, 1983. Copyright 1983, with permission from Elsevier.

and mast cells. Mediator release is triggered by antigen (allergen) interaction with Fc receptor-bound IgE, and the mediators released are responsible for the pathophysiologic changes of allergic diseases (Table 1-11). Mediators released from mast cells and basophils can be divided into three broad functional types: (1) those that increase vascular permeability and contract smooth muscle (histamine, platelet-activating factor, SRS-A, BK-A), (2) those that are chemotactic for or activate other inflammatory cells (ECF-A, NCF, leukotriene B_4), and (3) those that modulate the release of other mediators (BK-A, platelet-activating factor).

Cytotoxic reactions of antibody

In this type of immunologic injury, complement-fixing (C1-binding) antibodies against normal or foreign cells or tissues (IgM, IgG1, IgG2, IgG3) bind complement via the classic pathway and initiate a sequence of events similar to that initiated by immune-complex deposition, resulting in cell lysis or tissue injury. Examples of antibody-mediated cytotoxic reactions include red cell lysis in transfusion reactions, Goodpasture's syndrome with anti–glomerular basement membrane antibody formation, and pemphigus vulgaris with antiepidermal antibodies inducing blistering skin disease.

Classic delayed-type hypersensitivity reactions

Inflammatory reactions initiated by mononuclear leukocytes and not by antibody alone have been termed delayed-type hypersensitivity reactions. The term delayed has been used to contrast a secondary cellular response that appears 48–72 h after antigen exposure with an immediate hypersensitivity response generally seen within 12 h of antigen challenge and initiated by basophil mediator release or preformed antibody. For example, in an individual previously infected with M. tuberculosis organisms, intradermal placement of tuberculin purified protein derivative as a skin test challenge results in an indurated area of skin at 48–72 h, indicating previous exposure to tuberculosis.

The cellular events that result in classic delayed-type hypersensitivity responses are centered on T cells (predominantly, although not exclusively, IFN-γ, IL-2, and TNF-α-secreting T_H1-type helper T cells) and macrophages. Recently NK cells have been suggested to play a major role in the form of delayed hypersensitivity that occurs following skin contact with immunogens. First, local immune and inflammatory responses at the site of foreign antigen upregulate endothelial cell adhesion molecule expression, promoting the accumulation of lymphocytes at the tissue site. In the general schemes outlined in Figs. 1-2 and 1-3, antigen is processed by DCs and presented to small numbers of CD4+ T cells expressing a TCR specific for the antigen. IL-12 produced by APCs induces T cells to produce IFN-γ (T_H1 response). Macrophages frequently undergo epithelioid cell transformation and fuse to form multinucleated giant cells in response to IFN-γ. This type of mononuclear cell infiltrate is termed granulomatous inflammation. Examples of diseases in which delayed-type hypersensitivity plays a major role are fungal infections (histoplasmosis, mycobacterial infections (tuberculosis, leprosy, chlamydial infections (lymphogranuloma venereum, helminth infections (schistosomiasis, reactions to toxins (berylliosis, and hypersensitivity reactions to organic dusts (hypersensitivity pneumonitis. In addition, delayed-type hypersensitivity responses play important roles in tissue damage in autoimmune diseases such as rheumatoid arthritis, giant cell arteritis, and granulomatosis with polyangiitis (Wegener's) **(Chap. 11)**.

CLINICAL EVALUATION OF IMMUNE FUNCTION

Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defense and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells);

(2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement. Clinical problems that require an evaluation of immunity include chronic infections, recurrent infections, unusual infecting agents, and certain autoimmune syndromes. The type of clinical syndrome under evaluation can provide information regarding possible immune defects. Defects in cellular immunity generally result in viral, mycobacterial, and fungal infections. An extreme example of deficiency in cellular immunity is AIDS. Antibody deficiencies result in recurrent bacterial infections, frequently with organisms such as S. pneumoniae and Haemophilus in*fl*uenzae. Disorders of phagocyte function are frequently manifested by recurrent skin infections, often due to Staphylococcus aureus. Finally, deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent Neisseria infections (Table 1-16).

IMMUNOTHERAPY

Many therapies for autoimmune and inflammatory diseases involve the use of nonspecific immune-modulating or immunosuppressive agents such as glucocorticoids or cytotoxic drugs. The goal of development of new treatments for immune-mediated diseases is to design ways to specifically interrupt pathologic immune responses, leaving nonpathologic immune responses intact. Novel ways to interrupt pathologic immune responses that are under investigation include the use of anti-inflammatory cytokines or specific cytokine inhibitors as anti-inflammatory agents, the use of monoclonal antibodies against T or B lymphocytes as therapeutic agents, the use of intravenous Ig for certain infections and immune complex–mediated diseases, the use of specific cytokines to reconstitute components of the immune system, and bone marrow transplantation to replace the pathogenic immune system with a more normal immune system. In particular, the use of a monoclonal antibody to B cells (rituximab, anti-CD20 MAb) is approved in the United States for the treatment of non-Hodgkin's lymphoma and, in combination with methotrexate, for treatment of adult patients with severe rheumatoid arthritis resistant to TNF-α inhibitors **(Chap. 6)**. The U.S. Food and Drug Administration (FDA) approved the use of CTLA-4 antibodies in 2010 to block T cell anergy for use in cancer immunotherapy, and it was the first agent to demonstrate survival benefit in patients with advanced melanoma. Early-stage clinical trials have now shown that PD-1 blockade to reverse T cell exhaustion can induce tumor regression.

Cell-based therapies have been studied for many years, including ex vivo activation of NK cells for reinfusion into patients with malignancies and DC therapy of ex vivo priming of DCs for enhanced presentation of cancer antigens, with reinfusion of primed DCs into the patient. One such strategy for DC therapy has been approved by the FDA for treatment of advanced prostate cancer.

Cytokines and cytokine inhibitors

Several TNF inhibitors are used as biological therapies in the treatment of rheumatoid arthritis; these include monoclonal antibodies, TNF-R Fc fusion proteins, and Fab fragments. Use of anti-TNF-α antibody therapies such as adalimumab, infliximab, and golimumab has resulted in clinical improvement in patients with these diseases and has opened the way for targeting TNF-α to treat other severe forms of autoimmune and/or inflammatory disease. Blockage of TNF-α has been effective in rheumatoid arthritis, psoriasis, Crohn's disease, and ankylosing spondylitis. Other cytokine inhibitors are recombinant soluble TNF-α receptor (R) fused to human Ig and anakinra (soluble IL-1 receptor antagonist, or IL-1ra). The treatment of autoinflammatory syndromes (Table 1-6) with recombinant IL-1 receptor antagonist can prevent symptoms in these syndromes, because the overproduction of IL-1β is a hallmark of these diseases.

TNF-αR-Fc fusion protein (etanercept) and IL-1ra act to inhibit the activity of pathogenic cytokines in rheumatoid arthritis, i.e., TNF-α and IL-1, respectively. Similarly, anti-IL-6, IFN-β, and IL-11 act to inhibit pathogenic proinflammatory cytokines. Anti-IL-6 (tocilizumab) inhibits IL-6 activity, whereas IFN-β and IL-11 decrease IL-1 and TNF-α production.

Of particular note has been the successful use of IFN-γ in the treatment of the phagocytic cell defect in chronic granulomatous disease.

Monoclonal antibodies to T and B cells

The OKT3 MAb against human T cells has been used for several years as a T cell-specific immunosuppressive agent that can substitute for horse antithymocyte globulin (ATG) in the treatment of solid organ transplant rejection. OKT3 produces fewer allergic reactions than ATG but does induce human anti-mouse Ig antibody—thus limiting its use. Anti-CD4 MAb therapy has been used in trials to treat patients with rheumatoid arthritis. While inducing profound immunosuppression, anti-CD4 MAb treatment also induces susceptibility to severe infections. Treatment of patients with a MAb against the T cell molecule CD40 ligand (CD154) is under investigation to induce tolerance to organ transplants, with promising results reported in animal studies. Monoclonal antibodies to the CD25 (IL-2a) receptor (basiliximab) are being used for treatment of graft-versus-host disease in bone marrow transplantation, and anti-CD20 MAb (rituximab) is used to treat hematologic neoplasms, autoimmune diseases, kidney transplant rejection, and rheumatoid arthritis. The anti-IgE monoclonal antibody (omalizumab) is used for

blocking antigen-specific IgE that causes hay *f*ever and allergic rhinitis; however, side effects of anti-IgE include increased risk of anaphylaxis. Studies have shown that T_H17 cells, in addition to T_H1, are mediators of inflammation in Crohn's disease, and anti–IL-12/IL-23p40 antibody therapy has been studied as a treatment.

It is important to realize the potential risks of these immunosuppressive monoclonal antibodies. Natalizumab is a humanized IgG antibody against an a4 integrin that inhibits leukocyte migration into tissues and has been approved for treatment of multiple sclerosis in the United States. Both it and anti-CD20 (rituximab) have been associated with the onset of progressive multifocal leukoencephalopathy (PML)—a serious and usually fatal CNS infection caused by JC polyomavirus. Efalizumab, a humanized IgG monoclonal antibody previously approved for treatment of plaque psoriasis, has now been taken off the market due to reactivation of JC virus leading to fatal PML. Thus, use of any currently approved immunosuppressant immunotherapies should be undertaken with caution and with careful monitoring of patients according to FDA guidelines.

Tolerance induction

Specific immunotherapy has moved into a new era with the introduction of soluble CTLA-4 protein into clinical trials. Use of this molecule to block T cell activation via TCR/CD28 ligation during organ or bone marrow transplantation has showed promising results in animals and in early human clinical trials. Specifically, treatment of bone marrow with CTLA-4 protein reduces rejection of the graft in HLA-mismatched bone marrow transplantation. In addition, promising results with soluble CTLA-4 have been reported in the downmodulation of autoimmune T cell responses in the treatment of psoriasis; and it is being studied for treatment of systemic lupus erythematosus **(Chap. 4)**.

Intravenous immunoglobulin (IVIg)

IVIg has been used successfully to block reticuloendothelial cell function and immune complex clearance in various immune cytopenias such as immune thrombocytopenia. In addition, IVIg is useful for prevention of tissue damage in certain inflammatory syndromes such as Kawasaki disease and as Ig replacement therapy for certain types of immunoglobulin deficiencies. In addition, controlled clinical trials support the use of IVIg in selected patients with graft-versus-host disease, multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome, and chronic demyelinating polyneuropathy.

Stem cell transplantation

Hematopoietic stem cell transplantation (SCT) is now being comprehensively studied to treat several autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, and scleroderma. The goal of immune reconstitution in autoimmune disease syndromes is to replace a dysfunctional immune system with a normally reactive immune cell repertoire. Preliminary results in patients with scleroderma and lupus have showed encouraging results. Controlled clinical trials in these three diseases are now being launched in the United States and Europe to compare the toxicity and efficacy of conventional immunosuppression therapy with that of myeloablative autologous SCT. Recently, SCT was used in the setting of HIV-1 infection. HIV-1 infection of CD4+ T cells requires the presence of surface CD4 receptor and the chemokine receptor 5 (CCR5) co-receptor. Studies have demonstrated that patients who are homozygous for a 32-bp deletion in the CCR5 allele do not express CD4+ T cell CCR5 and thus are resistant to HIV-1 infection with HIV-1 strains that use this co-receptor. Stem cells from a homozygous CCR5 delta32 donor were transplanted to an HIV-infected patient following standard conditioning for such transplants, and the patient has maintained long-term control of the virus without antiretrovirals. Thus, a number of recent insights into immune system function have spawned a new field of interventional immunotherapy and have enhanced the prospect for development of more specific and nontoxic therapies for immune and inflammatory diseases.

CHAPTER 2

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Gerald T. Nepom

THE HLA COMPLEX AND ITS PRODUCTS

The human major histocompatibility complex (MHC), commonly called the human leukocyte antigen (HLA) complex, is a 4-megabase (Mb) region on chromosome 6 (6p21.3) that is densely packed with expressed genes. The best known of these genes are the HLA class I and class II genes, whose products are critical for immunologic specificity and transplantation histocompatibility, and they play a major role in susceptibility to a number of autoimmune diseases. Many other genes in the HLA region are also essential to the innate and antigen-specific functioning of the immune system. The HLA region shows extensive conservation with the MHC of other mammals in terms of genomic organization, gene sequence, and protein structure and function.

The HLA class I genes are located in a 2-Mb stretch of DNA at the telomeric end of the HLA region **(Fig. 2-1)**. The classic (MHC class Ia) HLA-A, -B, and -C loci, the products of which are integral participants in the immune response to intracellular infections, tumors, and allografts, are expressed in all nucleated cells and are highly polymorphic in the population. Polymorphism refers to a high degree of allelic variation within a genetic locus that leads to extensive variation between different individuals expressing different alleles. More than 2000 alleles at HLA-A, nearly 3000 alleles at HLA-B, and more than 1700 at HLA-C have been identified in different human populations, making this the most highly polymorphic segment known within the human genome. Each of the alleles at these loci encodes a heavy chain (also called an α chain) that associates noncovalently with the nonpolymorphic light chain β_2-microglobulin, encoded on chromosome 15.

The nomenclature of HLA genes and their products is based on a revised World Health Organization (WHO) nomenclature, in which alleles are given a single designation that indicates locus, allotype, and sequence-based subtype. For example, HLA-A*02:01 indicates subtype 1 of a group of alleles that encode HLA-A2 molecules. Subtypes that differ from each other at the nucleotide but not the amino acid sequence level are designated by an extra numeral (e.g., HLA-B*07:02:01 and HLA-B*07:02:02 are two variants of HLA-B*07:02, both encoding the same HLA-B7 molecule). The nomenclature of class II genes, discussed below, is made more complicated by the fact that both chains of a class II molecule are encoded by closely linked HLA-encoded loci, each of which may be polymorphic, and by the presence of differing numbers of isotypic DRB loci in different individuals. It has become clear that accurate HLA genotyping requires DNA sequence analysis, and the identification of alleles at the DNA sequence level has contributed greatly to the understanding of the role of HLA molecules as peptide-binding ligands, to the analysis of associations of HLA alleles with certain diseases, to the study of the population genetics of HLA, and to a clearer understanding of the contribution of HLA differences to allograft rejection and graft-versus-host disease. Current databases of HLA class I and class II sequences can be accessed by the Internet (e.g., from the IMGT/HLA Database, http://www.ebi.ac.uk/imgt/hla), and frequent updates of HLA gene lists are published in several journals.

The biologic significance of this MHC genetic diversity, resulting in extreme variation in the human population, is evident from the perspective of the structure of MHC molecules. As shown in **Fig. 2-2**, the MHC class I and class II genes encode MHC molecules that bind small peptides, and together this complex (pMHC; peptide-MHC) forms the ligand for recognition by T lymphocytes, through the antigen-specific T cell receptor (TCR). There is a direct link between the genetic variation and this structural interaction: The allelic changes in genetic sequence result in diversification of the peptide-binding capabilities of each MHC molecule and in differences for specific TCR binding.

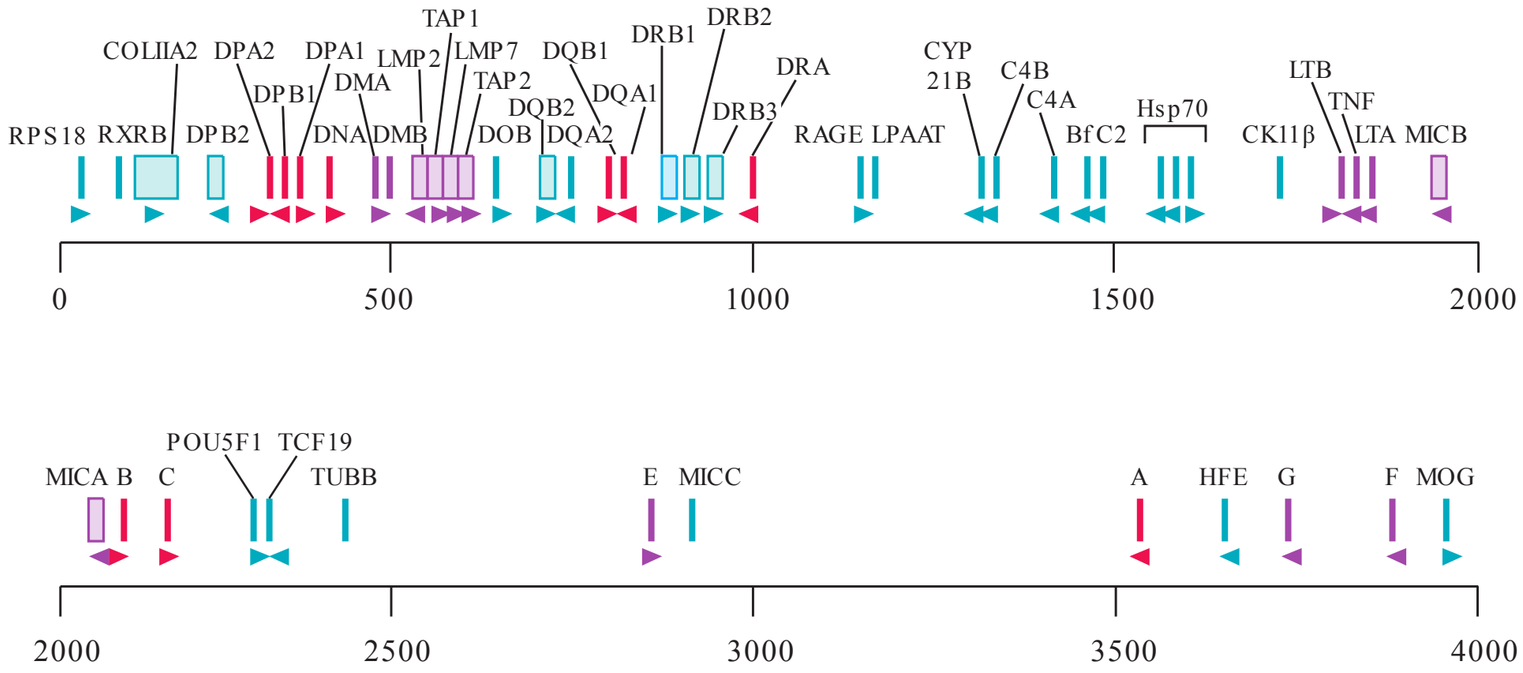


FIGURE 2-1

Physical map of the HLA region, showing the class I and class II loci, other immunologically important loci, and a sampling of other genes mapped to this region. Gene orientation is indicated by arrowheads. Scale is in kilobase (kb). The approximate genetic distance from DP to A is 3.2 cM. This includes 0.8 cM between A and B (including 0.2 cM between C and B), 0.4–0.8 cM between B and DR-DQ, and 1.6–2.0 cM between DR-DQ and DP.

Thus, different pMHC complexes bind different antigens and are targets for recognition by different T cells.

The class I MHC and class II MHC structures, shown in Fig. 2-2B, C, are structurally closely related; however, there are a few key differences. While both bind peptides and present them to T cells, the binding pockets have different shapes, which influence the types of immune responses that result (discussed below). In addition, there are structural contact sites for T cell molecules known as CD8 and CD4, expressed on the class I or class II membrane-proximal domains, respectively. This ensures that when peptide antigens are presented by class I molecules, the responding T cells are predominantly of the CD8 class, and similarly, that T cells responding to class II pMHC complexes are predominantly CD4.

The nonclassic, or class Ib, MHC molecules, HLA-E, -F, and -G, are much less polymorphic than MHC Ia and appear to have distinct functions. The HLA-E molecule has a peptide repertoire displaying signal peptides

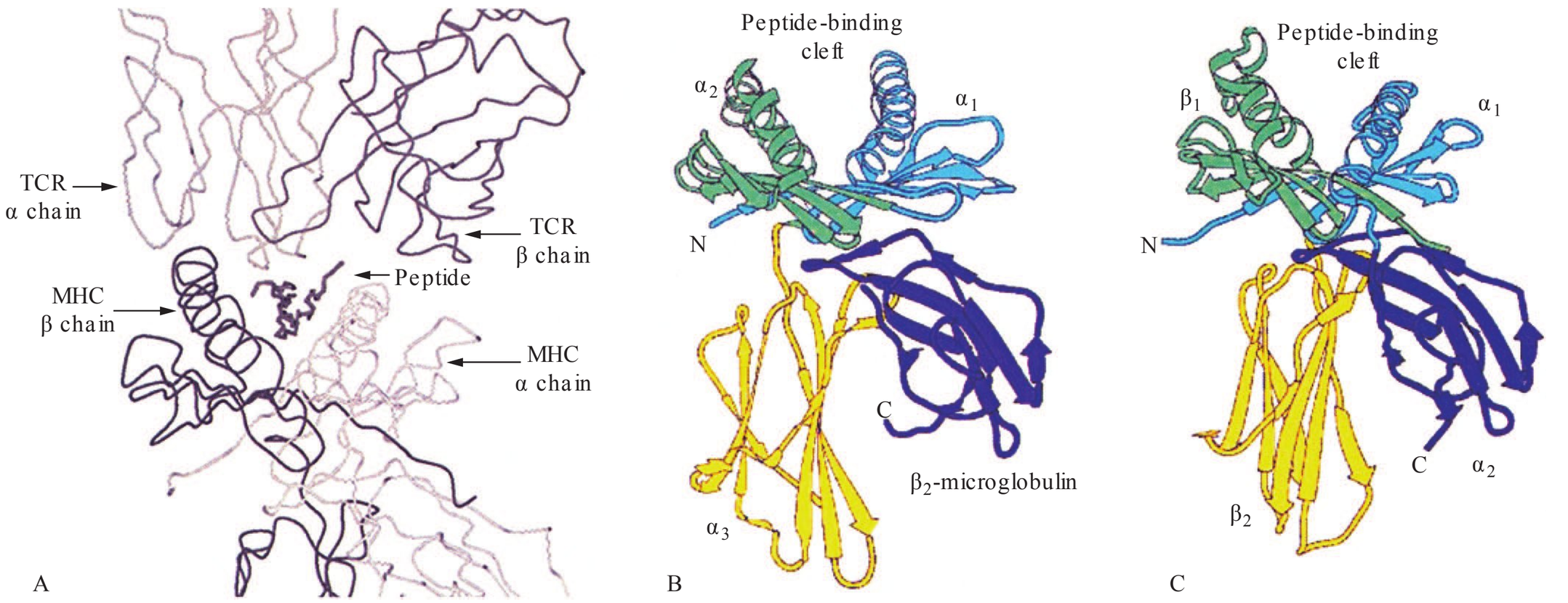


FIGURE 2-2

A. The trimolecular complex of TCR (top), MHC molecule (bottom), and a bound peptide form the structural determinants of specific antigen recognition. Other panels (B and C) show the domain structure of MHC class I (B) and class II (C) molecules. The α_1 and α_2 domains of class I and the α_1 and β_1 domains of class II form a β-sheet platform that forms the floor of the peptide-binding groove, and α helices that form the sides of the groove. The α_3 (B) and β_2 domains (C) project from the cell surface and form the contact sites for CD8 and CD4, respectively. (Adapted from EL Reinherz et al: Science 286:1913, 1999; and C Janeway et al: Immunobiology Bookshelf, 2nd ed. Garland Publishing, New York, 1997; with permission.)

cleaved from classic MHC class I molecules and is the major self-recognition target for the natural killer (NK) cell–inhibitory receptors NKG2A or NKG2C paired with CD94 (see below and **Chap. 1**). T is appears to be a function of immune surveillance, because loss of MHC class I signal peptides serves as a surrogate marker for injured or infected cells, leading to release of the inhibitory signal and subsequent activation of NK cells. HLA-E can also bind and present peptides to CD8 T cells, albeit with a limited scope, as only three HLA-E alleles are known. HLA-G is expressed mainly in stem cells and in extravillous trophoblasts, the fetal cell population directly in contact with maternal tissues. It binds a wide array of peptides, is expressed in six different alternatively spliced forms, and provides inhibitory signals to both NK cells and T cells, presumably in the service of maintaining maternofetal tolerance. Pathologic expression in cancer and infections may also deliver a similar inhibitory immunologic function; 16 HLA-G alleles have been identified. T e protein product of HLA-F is found mainly intracellularly, and the function of this locus, which encodes four alleles but has multiple transcriptional variations, remains largely unknown.

Additional class I–like genes have been identified, some HLA-linked and some encoded on other chromosomes, that show only distant homology to the class Ia and Ib molecules but share the three-dimensional class I structure. T ose on chromosome 6p21 include MIC-A and MIC-B, which are encoded centromeric to HLA-B, and HLA-HFE, located 3 to 4 cM (centiMorgan) telomeric of HLA-F. MIC-A and MIC-B do not bind peptide but are expressed on gut and other epithelium in a stress-inducible manner and serve as activation signals for certain γδ T cells, NK cells, CD8 T cells, and activated macrophages, acting through the activating NKG2D receptors. Ninety-one MIC-A and 40 MIC-B alleles are known, and additional diversification comes from variable alanine repeat sequences in the transmembrane domain. Due to this structural diversity, MIC-A can be recognized as a foreign tissue target during organ transplantation, contributing to graft failure. HLA-HFE encodes the gene defective in hereditary hemochromatosis. Among the non-HLA, class I–like genes, CD1 refers to a family of molecules that present glycolipids or other nonpeptide ligands to certain T cells, including T cells with NK activity; FcRn binds IgG within lysosomes and protects it from catabolism; and Zn-α_2-glycoprotein 1 binds a nonpeptide ligand and promotes catabolism of triglycerides in adipose tissue. Like the HLA-A, -B, -C, -E, -F, and -G heavy chains, each of which forms a heterodimer with β_2-microglobulin (Fig. 2-2), the class I–like molecules, HLA-HFE, FcRn, and CD1 also bind to β_2-microglobulin, but MIC-A, MIC-B, and Zn-α_2-glycoprotein 1 do not.

T e HLA class II region is also illustrated in Fig. 2-1. Multiple class II genes are arrayed within the centromeric 1 Mb of the HLA region, forming distinct haplotypes. A haplotype refers to an array of alleles at polymorphic loci along a chromosomal segment. Multiple class II genes are present on a single haplotype, clustered into three major subregions: HLA-DR, -DQ, and -DP. Each of these subregions contains at least one functional alpha (A) locus and one functional beta (B) locus. Together these encode proteins that form the α and β polypeptide chains of a mature class II HLA molecule. T us, the DRA and DRB genes encode an HLA-DR molecule; DQA and DQB genes encode HLA-DQ molecules; and DPA and DPB genes encode HLA-DP molecules. T ere are several DRB genes (DRB1, DRB2, DRB3, etc.), so that two expressed DR molecules are encoded on most haplotypes by combining the α-chain product of the DRA gene with separate β chains. More than 1000 alleles have been identified at the HLA-DRB1 locus, with most of the variation occurring within limited segments encoding residues that interact with antigens. Detailed analysis of sequences and population distribution of these alleles strongly suggest that this diversity is actively selected by environmental pressures associated with pathogen diversity. In the DQ region, both DQA1 and DQB1 are polymorphic, with 50 DQA1 alleles and over 300 DQB1 alleles. T e current nomenclature is largely analogous to that discussed above for class I, using the convention "locus * allele."

In addition to allelic polymorphism, products of different DQA alleles can, with some limitations, pair with products of different DQB alleles through both cis and trans pairing to create combinatorial complexity and expand the number of expressed class II molecules. Because of the enormous allelic diversity in the general population, most individuals are heterozygous at all of the class I and class II loci. T us, most individuals express six classic class I molecules (two each of HLA-A, -B, and -C) and many class II molecules—two DP, two to four DR, and multiple DQ (both cis and trans dimers).

OTHER GENES IN THE MHC

In addition to the class I and class II genes themselves, there are numerous genes interspersed among the HLA loci that have interesting and important immunologic functions. Our current concept of the function of MHC genes now encompasses many of these additional genes, some of which are also highly polymorphic. Indeed, direct comparison of the complete DNA sequences for eight of the entire 4-Mb MHC regions from different haplotypes show >44,000 nucleotide variations, encoding an extremely high potential for biologic diversity, and at least 97 genes located in this region are known to have coding region sequence variation. Specific

examples include the TAP and LMP genes, as discussed in more detail below, which encode molecules that participate in intermediate steps in the HLA class I biosynthetic pathway. Another set of HLA genes, DMA and DMB, perform an analogous function for the class II pathway. T ese genes encode an intracellular molecule that facilitates the proper complexing of HLA class II molecules with antigen (see below). T e HLA class III region is a name given to a cluster of genes between the class I and class II complexes, which includes genes for the two closely related cytokines tumor necrosis factor (TNF)-α and lymphotoxin (TNF-β); the complement components C2, C4, and Bf; heat shock protein (HSP) 70; and the enzyme 21-hydroxylase.

T e class I genes HLA-A, -B, and -C are expressed in all nucleated cells, although generally to a higher degree on leukocytes than on nonleukocytes. In contrast, the class II genes show a more restricted distribution: HLA-DR and HLA-DP genes are constitutively expressed on most cells of the myeloid cell lineage, whereas all three class II gene families (HLA-DR, -DQ, and -DP) are inducible by certain stimuli provided by inflammatory cytokines such as interferon γ. Within the lymphoid lineage, expression of these class II genes is constitutive on B cells and inducible on human T cells. Most endothelial and epithelial cells in the body, including the vascular endothelium and the intestinal epithelium, are also inducible for class II gene expression, and some cells show specialized expression, such as HLA-DQA2 and HLA-DQB2 on Langerhans cells. While somatic tissues normally express only class I and not class II genes, during times of local inflammation, they are recruited by cytokine stimuli to express class II genes as well, thereby becoming active participants in ongoing immune responses. Class II expression is controlled largely at the transcriptional level through a conserved set of promoter elements that interact with a protein known as CIITA. Cytokine-mediated induction of CIITA is a principal method by which tissue-specific expression of HLA gene expression is controlled. Other HLA genes involved in the immune response, such as TAP and LMP, are also susceptible to upregulation by signals such as interferon γ.

LINKAGE DISEQUILIBRIUM

In addition to extensive polymorphism at the class I and class II loci, another characteristic feature of the HLA complex is linkage disequilibrium. T is is formally defined as a deviation from Hardy-Weinberg equilibrium for alleles at linked loci. T is is reflected in the very low recombination rates between certain loci within the HLA complex. For example, recombination between DR and DQ loci is almost never observed in family studies, and characteristic haplotypes with particular arrays of DR and DQ alleles are found in every population. Similarly, the complement components C2, C4, and Bf are almost invariably inherited together, and the alleles at these loci are found in characteristic haplotypes. In contrast, there is a recombinational hotspot between DQ and DP, which are separated by 1–2 cM of genetic distance, despite their close physical proximity. Certain extended haplotypes encompassing the interval from DQ into the class I region are commonly found, the most notable being the haplotype DR3-B8-A1, which is found, in whole or in part, in 10–30% of northern European whites. It has been hypothesized that selective pressures may maintain linkage disequilibrium in HLA, but this remains to be determined. As discussed below under HLA and immunologic disease, one consequence of the phenomenon of linkage disequilibrium has been the resulting dif culty in assigning HLA-disease associations to a single allele at a single locus.

MHC STRUCTURE AND FUNCTION

Class I and class II molecules display a distinctive structural architecture, which contains specialized functional domains responsible for the unique genetic and immunologic properties of the HLA complex. T e principal known function of both class I and class II HLA molecules is to bind antigenic peptides in order to present antigen to an appropriate T cell. T e ability of a particular peptide to satisfactorily bind to an individual HLA molecule is a direct function of the molecular fit between the amino acid residues on the peptide with respect to the amino acid residues of the HLA molecule. T e bound peptide forms a tertiary structure called the MHC-peptide complex, which communicates with T lymphocytes through binding to the TCR molecule. T e first site of TCR-MHC-peptide interaction in the life of a T cell occurs in the thymus, where self-peptides are presented to developing thymocytes by MHC molecules expressed on thymic epithelium and hematopoietically derived antigen-presenting cells, which are primarily responsible for positive and negative selection, respectively **(Chap. 1)**. T us, the population of MHC–T cell complexes expressed in the thymus shapes the TCR repertoire. Mature T cells encounter MHC molecules in the periphery both in the maintenance of tolerance **(Chap. 3)** and in the initiation of immune responses. T e MHC-peptide-TCR interaction is the central event in the initiation of most antigen-specific immune responses, since it is the structural determinant of the specificity. For potentially immunogenetic peptides, the ability of a given peptide to be generated and bound by an HLA molecule is a primary feature of whether or not an immune response to that peptide can be generated, and the repertoire of peptides that a particular individual's HLA

molecules can bind exerts a major influence over the specificity of that individual's immune response.

When a TCR molecule binds to an HLA-peptide complex, it forms intermolecular contacts with both the antigenic peptide and with the HLA molecule itself. T e outcome of this recognition event depends on the density and duration of the binding interaction, accounting for a dual specificity requirement for activation of the T cell. T at is, the TCR must be specific both for the antigenic peptide and for the HLA molecule. T e polymorphic nature of the presenting molecules, and the influence that this exerts on the peptide repertoire of each molecule, results in the phenomenon of MHC restriction of the T cell specificity for a given peptide. T e binding of CD8 or CD4 molecules to the class I or class II molecule, respectively, also contributes to the interaction between T cell and the HLA-peptide complex, by providing for the selective activation of the appropriate T cell.

CLASS I STRUCTURE

(Fig. 2-2B) As noted above, MHC class I molecules provide a cell-surface display of peptides derived from intracellular proteins, and they also provide the signal for self-recognition by NK cells. Surface-expressed class I molecules consist of an MHC-encoded 44-kD glycoprotein heavy chain, a non-MHC-encoded 12-kD light chain β_2-microglobulin, and an antigenic peptide, typically 8–11 amino acids in length and derived from intracellularly produced protein. T e heavy chain displays a prominent peptide-binding groove. In HLA-A and -B molecules, the groove is □3 nm in length by 1.2 nm in maximum width (30 Å × 12 Å), whereas it is apparently somewhat wider in HLA-C. Antigenic peptides are noncovalently bound in an extended conformation within the peptide-binding groove, with both N- and C-terminal ends anchored in pockets within the groove (A and F pockets, respectively) and, in many cases, with a prominent kink, or arch, approximately one-third of the way from the N-terminus that elevates the peptide main chain off the floor of the groove.

A remarkable property of peptide binding by MHC molecules is the ability to form highly stable complexes with a wide array of peptide sequences. T is is accomplished by a combination of peptide sequence–independent and peptide sequence–dependent bonding. T e former consists of hydrogen bond and van der Waals interactions between conserved residues in the peptide-binding groove and charged or polar atoms along the peptide backbone. T e latter is dependent upon the six side pockets that are formed by the irregular surface produced by protrusion of amino acid side chains from within the binding groove. T e side chains lining the pockets interact with some of the peptide side chains. T e sequence polymorphism among different class I alleles and isotypes predominantly affects the residues that line these pockets, and the interactions of these residues with peptide residues constitute the sequence-dependent bonding that confers a particular sequence "motif" on the range of peptides that can bind any given MHC molecule.

CLASS I BIOSYNTHESIS

(Fig. 2-3A) T e biosynthesis of the classic MHC class I molecules reflects their role in presenting endogenous peptides. T e heavy chain is cotranslationally inserted into the membrane of the endoplasmic reticulum (ER), where it becomes glycosylated and associates sequentially with the chaperone proteins calnexin and ERp57. It then forms a complex with β_2-microglobulin, and this complex associates with the chaperone calreticulin and the MHC-encoded molecule tapasin, which physically links the class I complex to TAP, the MHC-encoded transporter associated with antigen processing. Meanwhile, peptides generated within the cytosol from intracellular proteins by the multisubunit, multicatalytic proteasome complex are actively transported into the ER by TAP, where they are trimmed by enzymes known as ER aminopeptidases. At this point, peptides with appropriate sequence complementarity bind specific class I molecules to form complete, folded heavy chain–β_2-microglobulin–peptide trimer complexes. T ese are transported rapidly from the ER, through the cis- and trans-Golgi where the N-linked oligosaccharide is further processed, and thence to the cell surface.

Most of the peptides transported by TAP are produced in the cytosol by proteolytic cleavage of intracellular proteins by the multisubunit, multicatalytic proteasome, and inhibitors of the proteasome dramatically reduce expression of class I–presented antigenic peptides. A thiol-dependent oxidoreductase ERp57, which mediates disulfide bond rearrangements, also appears to play an important role in folding the class I–peptide complex into a stable multicomponent molecule. T e MHC-encoded proteasome subunits LMP2 and LMP7 may influence the spectrum of peptides produced but are not essential for proteasome function.

CLASS I FUNCTION

Peptide antigen presentation

On any given cell, a class I molecule occurs in 100,000–200,000 copies and binds several hundred to several thousand distinct peptide species. T e vast majority of these peptides are self-peptides to which the host immune system is tolerant by one or more of the mechanisms that maintain tolerance (e.g., clonal deletion in the thymus or clonal anergy or clonal ignorance in the periphery **[Chaps. 1 and 3]**). However, class I molecules

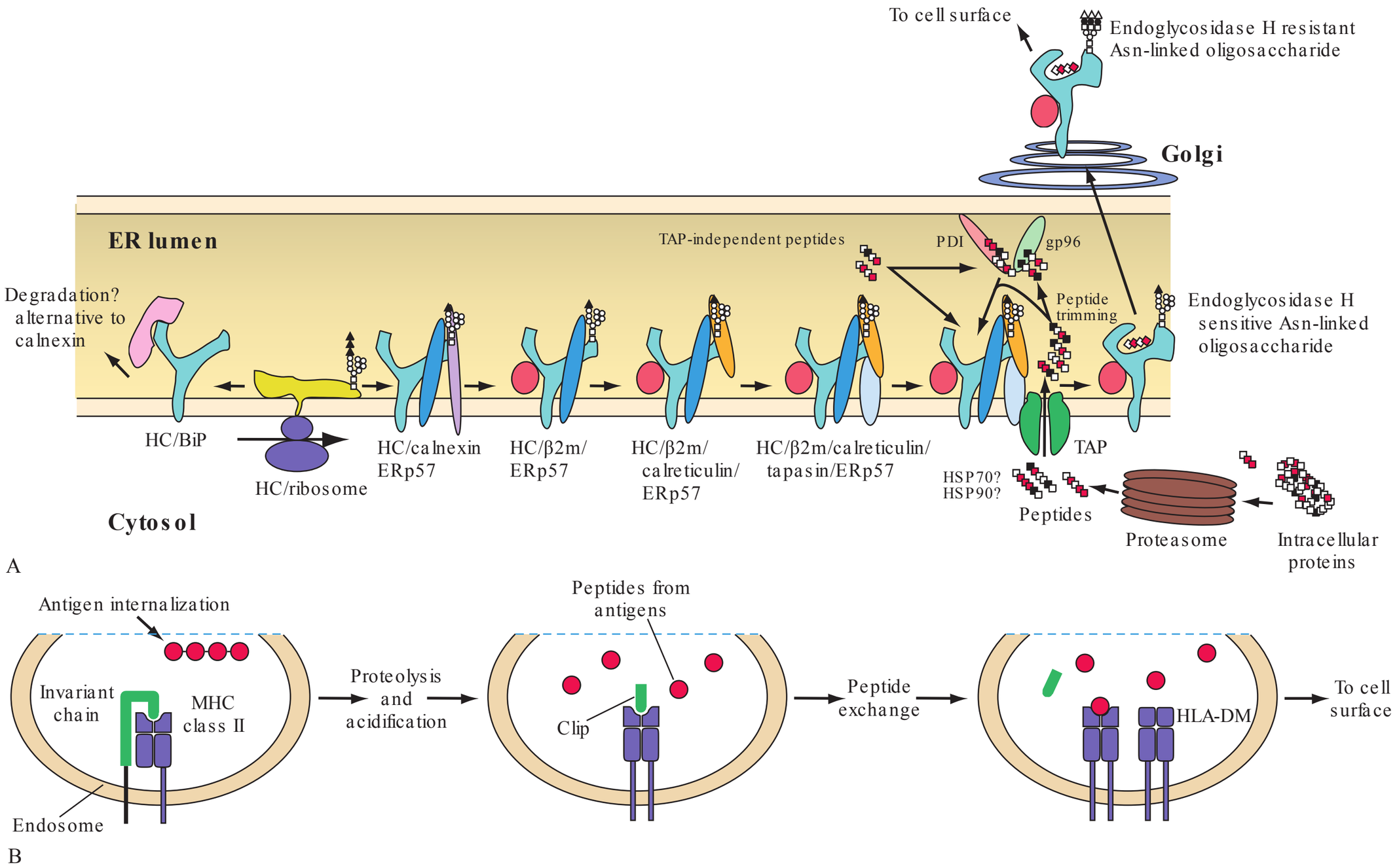


FIGURE 2-3

Biosynthesis of class I (A) and class II (B) molecules. A. Nascent heavy chain (HC) becomes associated with β_2-microglobulin (β2m) and peptide through interactions with a series of chaperones. Peptides generated by the proteasome are transported into the endoplasmic reticulum (ER) by TAP. Peptides undergo N-terminal trimming in the ER and become associated with chaperones, including gp96 and PDI. Once peptide binds to HC-β2m, the HC-β2m-peptide trimeric complex exits the ER and is transported by the secretory pathway to the cell surface. In the Golgi, the N-linked oligosaccharide undergoes maturation, with addition of sialic acid residues. Molecules are not necessarily drawn to scale. B. Pathway of HLA class II molecule assembly and antigen processing. After transport through the Golgi and post-Golgi compartment, the class II–invariant chain complex moves to an acidic endosome, where the invariant chain is proteolytically cleaved into fragments and displaced by antigenic peptides, facilitated by interactions with the DMA-DMB chaperone protein. This class II molecule–peptide complex is then transported to the cell surface.

bearing foreign peptides expressed in a permissive immunologic context activate CD8 T cells, which, if naïve, will then differentiate into cytolytic T lymphocytes (CTLs). T ese T cells and their progeny, through their αβ TCRs, are then capable of Fas/CD95- and/or perforin-mediated cytotoxicity and/or cytokine secretion **(Chap. 1)** upon further encounter with the class I–peptide combination that originally activated it, or other structurally related class I–peptide complexes. As alluded to above, this phenomenon by which T cells recognize foreign antigens in the context of specific MHC alleles is termed MHC restriction, and the specific MHC molecule is termed the restriction element. T e most common source of foreign peptides presented by class I molecules is viral infection, in the course of which peptides from viral proteins enter the class I pathway. T e generation of a strong CTL response that destroys virally infected cells represents an important antigen-specific defense against many viral infections **(Chap. 1)**. In the case of some viral infections—hepatitis B, for example—CTL-induced target cell apoptosis is thought to be a more important mechanism of tissue damage than any direct cytopathic effect of the virus itself. T e importance of the class I pathway in the defense against viral infection is underscored by the identification of a number of viral products that interfere with the normal class I biosynthetic pathway and thus block the immunogenetic expression of viral antigens.

Other examples of intracellularly generated peptides that can be presented by class I molecules in an immunogenic manner include peptides derived from nonviral intracellular infectious agents (e.g., Listeria, Plasmodium), tumor antigens, minor histocompatibility antigens, and certain autoantigens. T ere are also situations in which cell surface–expressed class I molecules are thought to acquire and present exogenously derived peptides.

HLA class I receptors and NK cell recognition

(Chap. 1) NK cells, which play an important role in innate immune responses, are activated to cytotoxicity and cytokine secretion by contact with cells that lack MHC class I expression, and NK cell activation is inhibited by cells that express MHC class I. In humans, the recognition of class I molecules by NK cells is carried out by three classes of receptor families, the killer cell–inhibitory cell receptor (KIR) family, the leukocyte Ig-like receptor (LIR) family, and the CD94/NKG2 family. The KIR family, also called CD158, is encoded on chromosome 19q13.4. KIR gene nomenclature is based on the number of domains (2D or 3D) and the presence of long (L) or short (S) cytoplasmic domains. The KIR2DL1 and S1 molecules primarily recognize alleles of HLA-C, which possess a lysine at position 80 (HLA-Cw2, -4, -5, and -6), whereas the KIR2DL2/S2 and KIR2DL3/S3 families primarily recognize alleles of HLA-C with asparagine at this position (HLA-Cw1, -3, -7, and -8). The KIR3DL1 and S1 molecules predominantly recognize HLA-B alleles that fall into the HLA-Bw4 class determined by residues 77–83 in the α_1 domain of the heavy chain, whereas the KIR3DL2 molecule is an inhibitory receptor for HLA-A*03. One of the KIR products, KIR2DL4, is known to be an activating receptor for HLA-G. The most common KIR haplotype in whites contains one activating KIR and six inhibitory KIR genes, although there is a great deal of diversity in the population, with >100 different combinations. It appears that most individuals have at least one inhibitory KIR for a self-HLA class I molecule, providing a structural basis for NK cell target specificity, which helps prevent NK cells from attacking normal cells. The importance of KIR-HLA interactions to many immune responses is illustrated by studies associating KIR3DL1 or S1 with multiple sclerosis, an autoimmune disease, but also with partial protection against HIV, in both cases consistent with a role for HLA-KIR mediated NK activation. Studies also show an association of KIR2DS1 with protection from relapse following allogeneic bone marrow transplantation in acute myeloid leukemia when these inhibitory receptors in the donors do not recognize the recipient HLA-C.

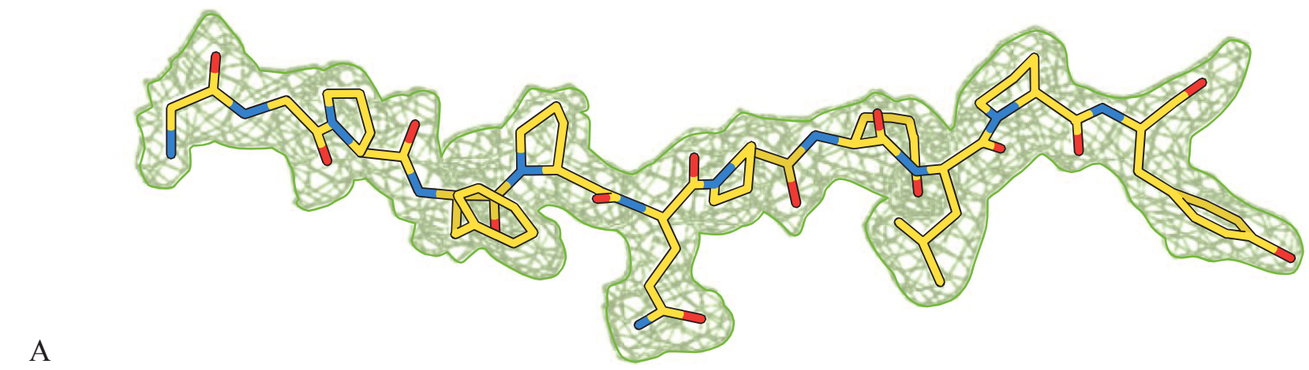
The LIR gene family (CD85, also called ILT) is encoded centromeric of the KIR locus on 19q13.4, and it encodes a variety of inhibitory immunoglobulin-like receptors expressed on many lymphocyte and other hematopoietic lineages. Interaction of LIR-1 (ILT2) with NK or T cells inhibits activation and cytotoxicity, mediated by many different HLA class I molecules, including HLA-G. HLA-F also appears to interact with LIR molecules, although the functional context for this is not understood.

The third family of NK receptors for HLA is encoded in the NK complex on chromosome 12p12.3-13.1 and consists of CD94 and five NKG2 genes, A/B, C, E/H, D, and F. These molecules are C-type (calcium-binding) lectins, and most function as disulfide-bonded heterodimers between CD94 and one of the NKG2 glycoproteins. The principal ligand of CD94/NKG2A receptors is the HLA-E molecule, complexed to a peptide derived from the signal sequence of classic HLA class I molecules and HLA-G. Thus, analogous to the way in which KIR receptors recognize HLA-C, the NKG2 receptor monitors self–class I expression, albeit indirectly through peptide recognition in the context of HLA-E. NKG2C, -E, and -H appear to have similar specificities but act as activating receptors. NKG2D is expressed as a homodimer and functions as an activating receptor expressed on NK cells, γδ TCR T cells, and activated CD8 T cells. When complexed with an adaptor called DAP10, NKG2D recognizes MIC-A and MIC-B molecules and activates the cytolytic response. NKG2D also binds a class of molecules known as ULBP, structurally related to class I molecules but not encoded in the MHC. **The function of NK cells in immune responses is discussed in Chap. 1**.

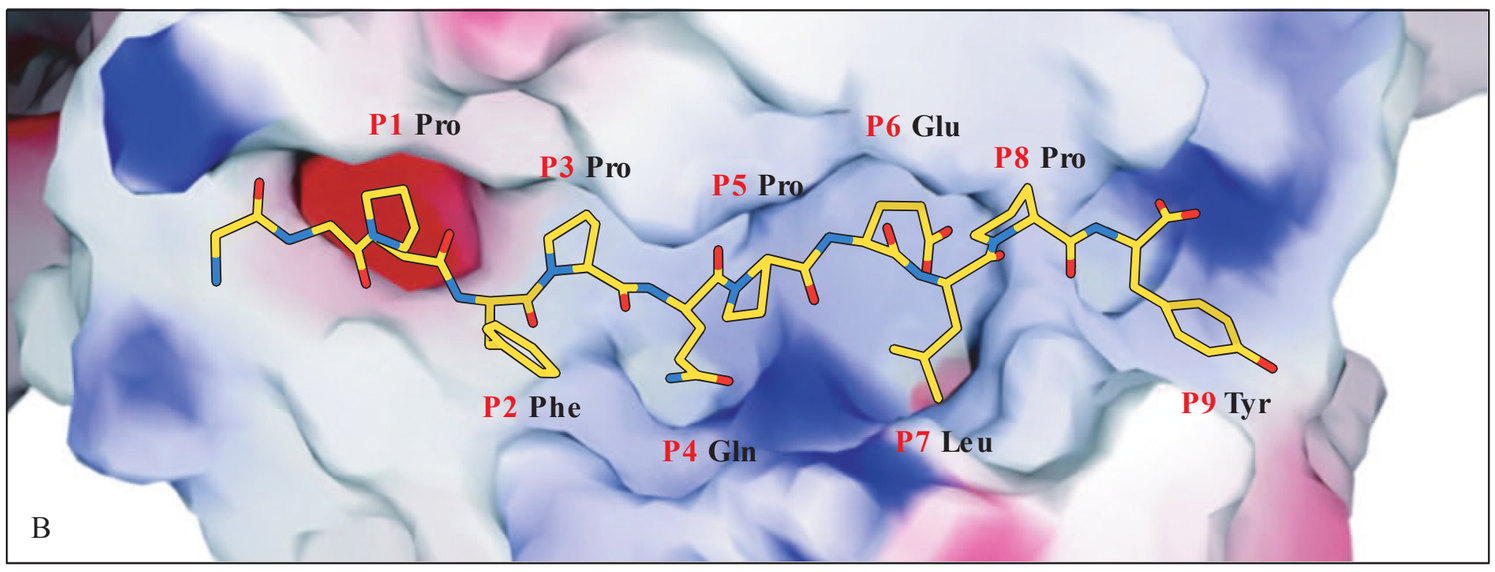
CLASS II STRUCTURE

(Fig. 2-2C) A specialized functional architecture similar to that of the class I molecules can be seen in the example of a class II molecule depicted in Fig. 2-2C, with an antigen-binding cleft arrayed above a supporting scaffold that extends the cleft toward the external cellular environment. However, in contrast to the HLA class I molecular structure, β_2-microglobulin is not associated with class II molecules. Rather, the class II molecule is a heterodimer, composed of a 29-kD α chain and a 34-kD β chain. The amino-terminal domains of each chain form the antigen-binding elements that, like the class I molecule, cradle a bound peptide in a groove bounded by extended α-helical loops, one encoded by the A (α chain) gene and one by the B (β chain) gene. Like the class I groove, the class II antigen-binding groove is punctuated by pockets that contact the side chains of amino acid residues of the bound peptide, but unlike the class I groove, it is open at both ends. Therefore, peptides bound by class II molecules vary greatly in length, since both the N- and C-terminal ends of the peptides can extend through the open ends of this groove. Approximately 11 amino acids within the bound peptide form intimate contacts with the class II molecule itself, with backbone hydrogen bonds and specific side chain interactions combining to provide, respectively, stability and specificity to the binding **(Fig. 2-4)**.

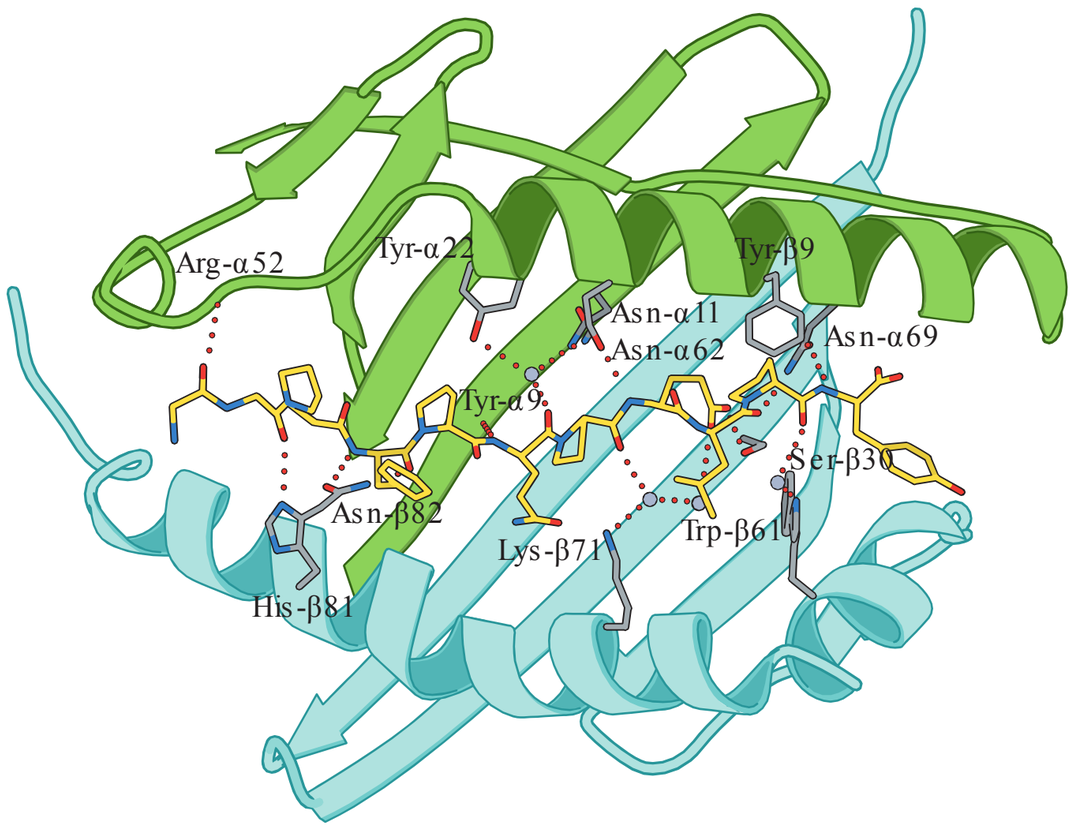
The genetic polymorphisms that distinguish different class II genes correspond to changes in the amino acid composition of the class II molecule, and these variable sites are clustered predominantly around the pocket structures within the antigen-binding groove. As with class I, this is a critically important feature of



A



B



C

FIGURE 2-4

Specif c intermolecular interactions determine peptide binding to MHC class II molecules. A short peptide sequence derived from alpha-gliadin (A) is accommodated within the MHC class II binding groove by specific interactions between peptide side chains (the P1–P9 residues illustrated in B) and corresponding pockets in the MHC class II structure. The latter are determined by the genetic polymorphisms of the MHC gene, in this case encoding an HLA-DQ2 molecule (C). This shows the extensive hydrogen bond and salt bridge network, which tightly constrains the pMHC complex and presents the complex of antigen and restriction element for CD4 T cell recognition. (From C Kim et al: Structural basis for HLA-DQ2-mediated presentation of gluten epitopes in celiac disease. Proc Natl Acad Sci USA 101:4175, 2004.)

the class II molecule, which explains how genetically different individuals have functionally different HLA molecules.

BIOSYNTHESIS AND FUNCTION OF CLASS II MOLECULES

(Fig. 2-3B) T e intracellular assembly of class II molecules occurs within a specialized compartmentalized pathway that differs dramatically from the class I pathway described above. As illustrated in Fig. 2-3B, the class II molecule assembles in the ER in association with a chaperone molecule, known as the invariant chain. T e invariant chain performs at least two roles. First, it binds to the class II molecule and blocks the peptide-binding groove, thus preventing antigenic peptides from binding. T is role of the invariant chain appears to account for one of the important

differences between class I and class II MHC pathways, since it can explain why class I molecules present endogenous peptides from proteins newly synthesized in the ER but class II molecules generally do not. Second, the invariant chain contains molecular localization signals that direct the class II molecule to traf c into post-Golgi compartments known as endosomes, which develop into specialized acidic compartments where proteases cleave the invariant chain, and antigenic peptides can now occupy the class II groove. T e specificity and tissue distribution of these proteases appear to be an important way in which the immune system regulates access to the peptide-binding groove and T cells become exposed to specific self-antigens. Differences in protease expression in the thymus and in the periphery may in part determine which specific peptide sequences comprise the peripheral repertoire for T cell recognition. It is at this stage in the intracellular pathway, after cleavage of the invariant chain, that the MHC-encoded DM molecule catalytically facilitates the exchange of peptides within the class II groove to help optimize the specificity and stability of the MHC-peptide complex.

Once this MHC-peptide complex is deposited in the outer cell membrane, it becomes the target for T cell recognition via a specific TCR expressed on lymphocytes. Because the endosome environment contains internalized proteins retrieved from the extracellular environment, the class II–peptide complex often contains bound antigens that were originally derived from extracellular proteins. In this way, the class II peptide–loading pathway provides a mechanism for immune surveillance of the extracellular space. T is appears to be an important feature that permits the class II molecule to bind foreign peptides, distinct from the endogenous pathway of class I–mediated presentation.

ROLE OF HLA IN TRANSPLANTATION

T e development of modern clinical transplantation in the decades since the 1950s provided a major impetus for elucidation of the HLA system, as allograft survival is highest when donor and recipient are HLA-identical. Although many molecular events participate in transplantation rejection, allogeneic differences at class I and class II loci play a major role. Class I molecules can promote T cell responses in several different ways. In the cases of allografts in which the host and donor are mismatched at one or more class I loci, host T cells can be activated by classic direct alloreactivity, in which the antigen receptors on the host T cells react with the foreign class I molecule expressed on the allograft. In this situation, the response of any given TCR may be dominated by the allogeneic MHC molecule, the peptide bound to it, or some combination of the two. Another type of host anti-graft T cell response involves the uptake and processing of donor MHC antigens by host antigen-presenting cells and the subsequent presentation of the resulting peptides by host MHC molecules. T is mechanism is termed indirect alloreactivity.

In the case of class I molecules on allografts that are shared by the host and the donor, a host T cell response may still be triggered because of peptides that are presented by the class I molecules of the graft but not of the host. T e most common basis for the existence of these endogenous antigen peptides, called minor histocompatibility antigens, is a genetic difference between donor and host at a non-MHC locus encoding the structural gene for the protein from which the peptide is derived. T ese loci are termed minor histocompatibility loci, and nonidentical individuals typically differ at many such loci. CD4 T cells react to analogous class II variation, both direct and indirect, and class II differences alone are suf cient to drive allograft rejection.

ASSOCIATION OF HLA ALLELES WITH SUSCEPTIBILITY TO DISEASE

It has long been postulated that infectious agents provide the driving force for the allelic diversification seen in the HLA system. An important corollary of this hypothesis is that resistance to specific pathogens may differ between individuals, based on HLA genotype. Observations of specific HLA genes associated with resistance to malaria or dengue fever, persistence of hepatitis B, and to disease progression in HIV infection are consistent with this model. For example, failure to clear persistent hepatitis B or C viral infection may reflect the inability of particular HLA molecules to present viral antigens effectively to T cells. Similarly, both protective and susceptible HLA allelic associations have been described for human papilloma virus–associated cervical neoplasia, implicating the MHC as an influence in mediating viral clearance in this form of cancer.

Pathogen diversity is probably also the major selective pressure favoring HLA heterozygosity. T e extraordinary scope of HLA allelic diversity increases the likelihood that most new pathogens will be recognized by some HLA molecules, helping to ensure immune fitness to the host. However, another consequence of diversification is that some alleles may become capable of recognition of “innocent bystander” molecules, including drugs, environmental molecules, and tissue-derived self-antigens. In a few instances, single HLA alleles display a strong selectivity for binding of a particular agent that accounts for a genetically determined response: Hypersensitivity to abacavir, an antiretroviral therapeutic, is directly linked to binding of abacavir in the antigen-binding pockets of HLA-B*57:01, where

it is buried underneath antigenic peptides and distorts the landscape, changing T cell recognition specificity; an adverse drug reaction to abacavir is more than 500 times more likely to occur in persons with HLA-B*57:01 than in individuals without this HLA allele. Another example is chronic beryllium toxicity, which is linked to binding of beryllium by HLA-DP molecules with a specific glutamic acid polymorphic residue on the class II beta chain. Even in the case of more complex diseases, particular HLA alleles are strongly associated with certain inappropriate immune-mediated disease states, particularly for some common autoimmune disorders **(Chap. 3)**. By comparing allele frequencies in patients with any particular disease and in control populations, >100 such associations have been identified, some of which are listed in **Table 2-1**. T e strength of genetic association is reflected in the term relative risk, which is a statistical odds ratio representing the risk of disease for an individual carrying a particular genetic marker compared with the risk for individuals in that population without that marker. T e nomenclature shown in Table 2-1 reflects both the HLA serotype (e.g., DR3, DR4) and the HLA genotype (e.g., DRB1*03:01, DRB1*04:01). It very likely the class I and class II alleles themselves are the true susceptibility alleles for most of these associations. However, because of the extremely strong linkage disequilibrium between the DR and DQ loci, in some cases it has been dif cult to determine the specific locus or combination of class II loci involved. In some cases, the susceptibility gene may be one of the HLA-linked genes located near the class I or class II region, but not the HLA gene itself, and in other cases, the susceptibility gene may be a non-HLA gene such as TNF-α, which is nearby. Indeed, since linkage disequilibrium of some haplotypes extends across large segments of the MHC region, it is quite possible that combinations of genes may account for the particular associations of HLA haplotypes with disease. For example, on some haplotypes associated with rheumatoid arthritis, both HLA-DRB1 alleles and a particular polymorphism associated with the TNF locus may be contributory to disease risk. Other candidates for similar epistatic effects include the IKBL gene and the MICA locus, potentially in combination with classic HLA class II risk alleles.

As might be predicted from the known function of the class I and class II gene products, almost all of the diseases associated with specific HLA alleles have an immunologic component to their pathogenesis. T e recent development of soluble HLA-peptide recombinant molecules as biological probes of T cell function, often in multivalent complexes referred to as "MHC tetramers," represents an opportunity to use HLA genetic associations to develop biomarkers for detection of early disease progression. However, it should be stressed that even the strong HLA associations with disease (those associations with relative risk of ≥10) implicate normal, rather than defective, alleles. Most individuals who carry these susceptibility genes do not express the associated disease; in this way, the particular HLA gene is permissive for disease but requires other environmental (e.g., the presence of specific antigens) or genetic factors for full penetrance. In each case studied, even in diseases with very strong HLA associations, the concordance of disease in monozygotic twins is higher than in HLA-identical dizygotic twins or other sibling pairs, indicating that non-HLA genes contribute to susceptibility and can significantly modify the risk attributable to HLA.

Another group of diseases is genetically linked to HLA, not because of the immunologic function of HLA alleles but rather because they are caused by autosomal dominant or recessive abnormal alleles at loci that happen to reside in or near the HLA region. Examples of these are 21-hydroxylase deficiency, hemochromatosis, and spinocerebellar ataxia.

CLASS I ASSOCIATIONS WITH DISEASE

Although the associations of human disease with particular HLA alleles or haplotypes predominantly involve the class II region, there are also several prominent disease associations with class I alleles. T ese include the association of Behçet's disease **(Chap. 12)** with HLA-B51, psoriasis vulgaris with HLA-Cw6, and, most notably, the spondyloarthritides **(Chap. 10)** with HLA-B27. Twenty-five HLA-B locus alleles, designated HLA-B*27:01–B*27:25, encode the family of B27 class I molecules. All of the subtypes share a common B pocket in the peptide-binding groove—a deep, negatively charged pocket that shows a strong preference for binding the arginine side chain. In addition, B27 is among the most negatively charged of HLA class I heavy chains, and the overall preference is for positively charged peptides. HLA-B*27:05 is the predominant subtype in whites and most other non-Asian populations, and this subtype is very highly associated with ankylosing spondylitis (AS) **(Chap. 10)**, both in its idiopathic form and in association with chronic inflammatory bowel disease or psoriasis vulgaris. It is also associated with reactive arthritis (ReA) **(Chap. 10)**, with other idiopathic forms of peripheral arthritis (undifferentiated spondyloarthropathy), and with recurrent acute anterior uveitis. B27 is found in 50–90% of individuals with these conditions, compared with a prevalence of □7% in North American whites.

It can be concluded that the B27 molecule itself is involved in disease pathogenesis, based on strong evidence from clinical epidemiology and on the occurrence of a spondyloarthropathy-like disease in HLA-B27 transgenic rats. T e association of B27 with these diseases may derive from the specificity of a particular peptide

TABLE 2-1

SIGNIFICANT HLA CLASS I AND CLASS II ASSOCIATIONS WITH DISEASE

	MARKER	GENE	STRENGTH OF ASSOCIATION
Spondyloarthropathies			
Ankylosing spondylitis	B27	B*27:02,–04, –05	++++
Reactive arthritis	B27		++++
Acute anterior uveitis	B27		+++
Reactive arthritis (Yersinia, Salmonella, Shigella, Chlamydia)	B27		+++
Psoriatic spondylitis	B27		+++
Collagen-Vascular Diseases			
Juvenile arthritis, pauciarticular	DR8 DR5		++ ++
Rheumatoid arthritis	DR4	DRB1*04:01,–04,–05	+++
Sjögren's syndrome	DR3		++
Systemic lupus erythematosus White Japanese	 DR3 DR2		 + ++
Autoimmune Gut and Skin			
Gluten-sensitive enteropathy (celiac disease)	DQ2	DQA1*05:01 DQB1*02:01	+++
Chronic active hepatitis	DR3		++
Dermatitis herpetiformis	DR3		+++
Psoriasis vulgaris	Cw6		++
Pemphigus vulgaris	DR4 DQ1	DRB1*04:02 DQB1*05:03	+++
Bullous pemphigoid variant	DQ7	DQB1*03:01	+
Autoimmune Endocrine			
Type 1 diabetes mellitus	DQ8 DR4 DR3 DR2	DQB1*03:02 DRB1*04:01,–04 DQB1*06:02	+++ ++ —[a]
Hyperthyroidism (Graves')	B8 DR3		+ +
Hyperthyroidism (Japanese)	B35		+
Adrenal insuf ciency	DR3		++
Autoimmune Neurologic			
Myasthenia gravis	B8		+
Multiple sclerosis	DR2 DR2	DRB1*15:01 DRB5*01:01	+ ++
Other			
Behçet's disease	B51		++
Congenital adrenal hyperplasia	B47	21•OH (Cyp21B)	+++
Narcolepsy	DR2	DQB1*06:02	++++
Goodpasture's syndrome (anti-GBM)	DR2		++
Abacavir hypersensitivity	B57	B*57:01	++++

[a]Strong negative association, i.e., genetic association with protection from diabetes.
Abbreviation: GBM, glomerular basement membrane.

or family of peptides bound to B27 or through another mechanism that is independent of the peptide specificity of B27. In particular, HLA-B27 has been shown to form heavy chain homodimers, utilizing the cysteine residue at position 67 of the B57 α chain, in the absence of β_2-microglobulin. T ese homodimers are expressed on the surface of lymphocytes and monocytes from patients with AS, and receptors including KIR3DL1, KIR3DL2, and ILT4 (LILRB2) are capable of binding to them, promoting the activation and survival of cells expressing these receptors. Alternatively, this dimerization "misfolding" of B27 may initiate an intracellular stress signaling response, called the unfolded protein response (UPR), capable of modulating immune cell function, possibly in enthesial-resident T cells that act as sensors of damage and environmental stress.

CLASS II DISEASE ASSOCIATIONS

As can be seen in Table 2-1, the majority of associations of HLA and disease are with class II alleles. Several diseases have complex HLA genetic associations.

Celiac disease

In the case of celiac disease, it is probable that the HLA-DQ genes are the primary basis for the disease association. HLA-DQ genes present on both the celiac-associated DR3 and DR7 haplotypes include the DQB1*02:01 gene, and further detailed studies have documented a specific class II αβ dimer encoded by the DQA1*05:01 and DQB1*02:01 genes, which appears to account for most of the HLA genetic contribution to celiac disease susceptibility. T is specific HLA association with celiac disease may have a straightforward explanation: Peptides derived from the wheat gluten component gliaden are bound to the molecule encoded by DQA1*05:01 and DQB1*02:01 and presented to T cells. Gliaden-derived peptides that are implicated in this immune activation bind the DQ class II dimer best when the peptide contains a glutamine to glutamic acid substitution. It has been proposed that tissue transglutaminase, an enzyme present at increased levels in the intestinal cells of celiac patients, converts glutamine to glutamic acid in gliadin, creating peptides that are capable of being bound by the DQ2 molecule and presented to T cells.

Pemphigus vulgaris

In the case of pemphigus vulgaris, there are two HLA genes associated with disease, DRB1*04:02 and DQB1*05:03. Peptides derived from desmoglein-3, an epidermal autoantigen, bind to the DRB1*04:02- and DQB1*05:03-encoded HLA molecules, and this combination of specific peptide binding and disease-associated class II molecule is suf cient to stimulate desmoglein-specific T cells. A bullous pemphigoid clinical variant, not involving desmoglein recognition, has been found to be associated with HLA-DQB1*03:01.

Juvenile arthritis

Pauciarticular juvenile arthritis **(Chap. 6)** is an autoimmune disease associated with genes at the DRB1 locus and also with genes at the DPB1 locus. Patients with both DPB1*02:01 and a DRB1 susceptibility allele (usually DRB1*08 or -*05) have a higher relative risk than expected from the additive effect of those genes alone. In juvenile patients with rheumatoid factor–positive polyarticular disease, heterozygotes carrying both DRB1*04:01 and -*04:04 have a relative risk >100, reflecting an apparent synergy in individuals inheriting both of these susceptibility genes.

Type 1 diabetes mellitus

Type 1 (autoimmune) diabetes mellitus is associated with MHC genes on more than one haplotype. T e presence of both the DR3 and DR4 haplotypes in one individual confers a twentyfold increased risk for type 1 diabetes; the strongest single association is with DQB1*03:02, and all haplotypes that carry a DQB1*03:02 gene are associated with type 1 diabetes, whereas related haplotypes that carry a different DQB1 gene are not. However, the relative risk associated with inheritance of this gene can be modified, depending on other HLA genes present either on the same or a second haplotype. For example, the presence of a DR2-positive haplotype containing a DQB1*06:02 gene is associated with decreased risk. T is gene, DQB1*06:02, is considered "protective" for type 1 diabetes. Even some DRB1 genes that can occur on the same haplotype as DQB1*03:02 may modulate risk, so that individuals with the DR4 haplotype that contains DRB1*04:03 are less susceptible to type 1 diabetes than individuals with other DR4-DQB1*03:02 haplotypes. T ere are some characteristic structural features of the diabetes-associated DQ molecule encoded by DQB1*03:02, particularly the capability for binding peptides that have negatively charged amino acids near their C-termini. T is may indicate a role for specific antigenic peptides or T cell interactions in the immune response to islet-associated proteins.

Although the presence of a DR3 haplotype in combination with the DR4-DQB1*0302 haplotype is a very high-risk combination for diabetes susceptibility, the specific gene on the DR3 haplotype that is responsible for this synergy is not yet identified.

Rheumatoid arthritis

T e HLA genes associated with rheumatoid arthritis (RA) **(Chap. 6)** encode a distinctive sequence of amino acids from codons 67–74 of the DRβ molecule: RA-associated

class II molecules carry the sequence LeuLeuGluGlnArgArgAlaAla or LeuLeuGluGlnLysArgAlaAla in this region, whereas non-RA-associated genes carry one or more differences in this region. T ese residues form a portion of the molecule that lies in the middle of the α-helical portion of the DRB1-encoded class II molecule, termed the shared epitope.

T e highest risk for susceptibility to RA comes in individuals who carry both a DRB1*04:01 and DRB1*04:04 gene. T ese DR4-positive RA-associated alleles with the shared epitope are most frequent among patients with more severe, erosive disease. Several mechanisms have been proposed that link the shared epitope to immune reactivity in RA. T is portion of the class II molecule may allow preferential binding of an arthritogenic peptide, it may favor the expansion of a type of self-reactive T lymphocyte, or it may itself form part of the pMHC ligand recognized by TCR that initiates synovial tissue recognition.

MOLECULAR MECHANISMS FOR HLA-DISEASE ASSOCIATIONS

As noted above, HLA molecules play a key role in the selection and establishment of the antigen-specific T cell repertoire and a major role in the subsequent activation of those T cells during the initiation of an immune response. Precise genetic polymorphisms characteristic of individual alleles dictate the specificity of these interactions and thereby instruct and guide antigen-specific immune events. T ese same genetically determined pathways are therefore implicated in disease pathogenesis when specific HLA genes are responsible for autoimmune disease susceptibility.

T e fate of developing T cells within the thymus is determined by the af nity of interaction between TCR and HLA molecules bearing self-peptides, and thus the particular HLA types of each individual control the precise specificity of the T cell repertoire **(Chap. 1)**. T e primary basis for HLA-associated disease susceptibility may well lie within this thymic maturation pathway. T e positive selection of potentially autoreactive T cells, based on the presence of specific HLA susceptibility genes, may establish the threshold for disease risk in a particular individual.

At the time of onset of a subsequent immune response, the primary role of the HLA molecule is to bind peptide and present it to antigen-specific T cells. T e HLA complex can therefore be viewed as encoding genetic determinants of precise immunologic activation events. Antigenic peptides that bind particular HLA molecules are capable of stimulating T cell immune responses; peptides that do not bind are not presented to T cells and are not immunogenic. T is genetic control of the immune response is mediated by the polymorphic sites within the HLA antigen–binding groove that interact with the bound peptides. In autoimmune and immune-mediated diseases, it is likely that specific tissue antigens that are targets for pathogenic lymphocytes are complexed with the HLA molecules encoded by specific susceptibility alleles. In autoimmune diseases with an infectious etiology, it is likely that immune responses to peptides derived from the initiating pathogen are bound and presented by particular HLA molecules to activate T lymphocytes that play a triggering or contributory role in disease pathogenesis. T e concept that early events in disease initiation are triggered by specific HLA-peptide complexes offers some prospects for therapeutic intervention, since it may be possible to design compounds that interfere with the formation or function of specific HLA-peptide–TCR interactions.

When considering mechanisms of HLA associations with immune response and disease, it is well to remember that just as HLA genetics are complex, so are the mechanisms likely to be heterogeneous. Immune-mediated disease is a multistep process in which one of the HLA-associated functions is to establish a repertoire of potentially reactive T cells, whereas another HLA-associated function is to provide the essential peptide-binding specificity for T cell recognition. For diseases with multiple HLA genetic associations, it is possible that both of these interactions occur and synergize to advance an accelerated pathway of disease.

CHAPTER 3

AUTOIMMUNITY AND AUTOIMMUNE DISEASES

Betty Diamond ■ Peter E. Lipsky

One of the central features of the immune system is the capacity to mount an inflammatory response to potentially harmful foreign materials while avoiding damage to self-tissues. Whereas recognition of self plays an important role in shaping the repertoires of immune receptors on both T and B cells and in clearing apoptotic and other tissue debris from sites throughout the body, the development of potentially harmful immune responses to self-antigens is, in general, prohibited. T e essential feature of an autoimmune disease is that tissue injury is caused by the immunologic reaction of the organism against its own tissues. Autoimmunity, on the other hand, refers merely to the presence of antibodies or T lymphocytes that react with self-antigens and does not necessarily imply that the self-reactivity has pathogenic consequences. Autoimmunity is present in all individuals; however, autoimmune disease occurs only in those individuals in whom the breakdown of one or more of the basic mechanisms regulating immune tolerance results in self-reactivity that can cause tissue damage.

Autoimmunity is seen in normal individuals, with a higher frequency among normal older people. Polyreactive autoantibodies that recognize many host antigens are present throughout life. Expression of these autoantibodies may be increased after some inciting events. T ese antibodies are usually of the IgM heavy chain isotype and are encoded by nonmutated germline immunoglobulin variable region genes. When autoimmunity is induced by an inciting event, such as infection or tissue damage from trauma or ischemia, the autoreactivity is in general self-limited. When such autoimmunity does persist, however, pathology may or may not result. Even in the presence of organ pathology, it may be difficult to determine whether the damage is mediated by autoreactivity. After an inciting event, the development of self-reactivity may be the consequence of an ongoing pathologic process, may be nonpathogenic, or may contribute to tissue inflammation and damage. Individuals with autoimmune disease may have numerous autoantibodies, only some or even none of which may be pathogenic. Patients with systemic sclerosis may have a wide array of antinuclear antibodies that are important in disease classification but are not clearly pathogenic; patients with pemphigus may also exhibit a wide array of autoantibodies, only one of which (antibody to desmoglein) is known to be pathogenic.

MECHANISMS OF AUTOIMMUNITY

Since Ehrlich first postulated the existence of mechanisms to prevent the generation of self-reactivity in the early 1900s, ideas concerning the nature of this prohibition have developed in parallel with a progressive increase in understanding of the immune system. Burnet's clonal selection theory included the idea that interaction of lymphoid cells with their specific antigens during fetal or early postnatal life would lead to elimination of such "forbidden clones." T is idea was refuted, however, when it was shown that autoimmune diseases could be induced in experimental animals by simple immunization procedures, that autoantigen-binding cells could be demonstrated easily in the circulation of normal individuals, and that self-limited autoimmune phenomena frequently developed after tissue damage from infection or trauma. T ese observations indicated that clones of cells capable of responding to autoantigens were present in the repertoire of antigen-reactive cells in normal adults and suggested that mechanisms in addition to clonal deletion were responsible for preventing their activation.

Currently, three general processes are thought to be involved in the maintenance of selective unresponsiveness to autoantigens **(Table 3-1)**: (1) sequestration of self-antigens, rendering them inaccessible to the immune system; (2) specific unresponsiveness (tolerance or anergy) of relevant T or B cells; and

TABLE 3-1

MECHANISMS PREVENTING AUTOIMMUNITY

1. Sequestration of self-antigens
2. Generation and maintenance of tolerance
   a. Central deletion of autoreactive lymphocytes
   b. Peripheral anergy of autoreactive lymphocytes
   c. Receptor replacement in autoreactive lymphocytes
3. Regulatory mechanisms
   a. Regulatory T cells
   b. Regulatory B cells
   c. Regulatory mesenchymal cells
   d. Regulatory cytokines
   e. Idiotype network

(3) limitation of potential reactivity by regulatory mechanisms. Derangements of these normal processes may predispose to the development of autoimmunity **(Table 3-2)**. In general, these abnormal responses require both an exogenous trigger, such as bacterial or viral infection or cigarette smoking, and the presence of endogenous abnormalities in the cells of the immune system. Microbial superantigens, such as staphylococcal protein A and staphylococcal enterotoxins, are substances that can stimulate a broad range of T and B cells through specific interactions with selected families of immune receptors, irrespective of their antigen specificity. If autoantigen-reactive T and/or B cells express these receptors, autoimmunity may develop.

TABLE 3-2

MECHANISMS OF AUTOIMMUNITY

I. Exogenous
   A. Molecular mimicry
   B. Superantigenic stimulation
   C. Microbial and tissue damage–associated adjuvanticity
II. Endogenous
   A. Altered antigen presentation
      1. Loss of immunologic privilege
      2. Presentation of novel or cryptic epitopes (epitope spreading)
      3. Alteration of self-antigen
      4. Enhanced function of antigen-presenting cells
         a. Costimulatory molecule expression
         b. Cytokine production
   B. Increased T cell help
      1. Cytokine production
      2. Costimulatory molecules
   C. Increased B cell function
      1. B cell activating factor
      2. Costimulatory molecules
   D. Apoptotic defects or defects in clearance of apoptotic material
   E. Cytokine imbalance
   F. Altered immunoregulation
   G. Endocrine abnormalities

Alternatively, molecular mimicry or cross-reactivity between a microbial product and a self-antigen may lead to activation of autoreactive lymphocytes. One of the best examples of autoreactivity and autoimmune disease resulting from molecular mimicry is rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins as well as with neuronal antigens. Deposition of these autoantibodies in the heart initiates an inflammatory response, whereas their penetration into the brain can result in Sydenham's chorea. Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, and multiple sclerosis. It is presumed that infectious agents may be able to overcome self-tolerance because they possess pathogen-associated molecular patterns (PAMPs). T ese molecules (e.g., bacterial endotoxin, RNA, or DNA) exert adjuvant-like effects on the immune system by interacting with Toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) that increase the immunogenicity and immunostimulatory capacity of the microbial material. T e adjuvants activate dendritic cells through TLRs, which in turn stimulate the activation of previously quiescent lymphocytes that recognize both microbial antigens and self-antigens. Similarly, cellular and tissue damage due to the release of damage-associated molecular patterns (DAMPs), including DNA, RNA nucleosomes, and other tissue debris, may activate cells of the inflammatory and immune systems through engagement of the same array of PRRs.

Endogenous derangements of the immune system may also contribute to the loss of immunologic tolerance to self-antigens and the development of autoimmunity (Table 3-2). Some autoantigens reside in immunologically privileged sites, such as the brain or the anterior chamber of the eye. These sites are characterized by the inability of engrafted tissue to elicit immune responses. Immunologic privilege results from a number of events, including the limited entry of proteins from those sites into lymphatics, the local production of immunosuppressive cytokines such as transforming growth factor β, and the local expression of molecules (including Fas ligand) that can induce apoptosis of activated T cells. Lymphoid cells remain in a state of immunologic ignorance (neither activated nor anergized) with regard to proteins expressed uniquely in immunologically privileged sites. If the privileged site is damaged by trauma or inflammation or if T cells are activated elsewhere, proteins expressed at this site can become immunogenic and also be the targets of immunologic assault. In multiple sclerosis and sympathetic ophthalmia, for example, antigens uniquely expressed in the brain and eye, respectively, become the target of activated T cells.

Alterations in antigen presentation may also contribute to autoimmunity. Peptide determinants (epitopes) of a self-antigen that are not routinely presented to lymphocytes may be recognized as a result of altered proteolytic processing of the molecule and the ensuing presentation of novel peptides (cryptic epitopes). When B cells rather than dendritic cells present self-antigen, they may also present cryptic epitopes that can activate autoreactive T cells. T ese cryptic epitopes will not previously have been available to effect the silencing of autoreactive lymphocytes. Furthermore, once there is immunologic recognition of one protein component of a multimolecular complex, reactivity may be induced to other components of the complex after internalization and presentation of all molecules within the complex (epitope spreading). Finally, inflammation, environmental agents, drug exposure, or normal senescence may cause a post-transitional alteration in proteins, resulting in the generation of immune responses that cross-react with normal self-proteins. For example, the induction and/or release of protein arginine deiminase enzymes results in the conversion of arginine residues to citrullines in a variety of proteins, thereby altering their capacity to induce immune responses. Production of antibodies to citrullinated proteins has been observed in rheumatoid arthritis and chronic lung disease as well as in normal smokers and may contribute to organ pathology. Alterations in the availability and presentation of autoantigens may be important components of immunoreactivity in certain models of organ-specific autoimmune diseases. In addition, these factors may be relevant to an understanding of the pathogenesis of various drug-induced autoimmune conditions. However, the diversity of autoreactivity manifesting in non-organ-specific systemic autoimmune diseases suggests that these conditions may result from a more general activation of the immune system rather than from an alteration in individual self-antigens.

Many autoimmune diseases are characterized by the presence of antibodies that react with apoptotic material. Defects in the clearance of apoptotic material have been shown to elicit auto-immunity and autoimmune disease in a number of animal models. Moreover, such defects have been found in patients with systemic lupus erythematosus (SLE). Apoptotic debris that is not cleared quickly by the immune system can function as endogenous ligands for a number of PRRs on dendritic cells and B cells. Under such circumstances, dendritic cells and/or B cells are activated, and an immune response to apoptotic debris can develop. In addition, the presence of extracellular apoptotic material within germinal centers of secondary lymphoid organs in patients with SLE may facilitate the direct activation of autoimmune B cell clones or may function to select such clones during immune responses.

Studies in a number of experimental models have suggested that intense stimulation of T lymphocytes can produce nonspecific signals that bypass the need for antigen-specific helper T cells and lead to polyclonal B cell activation with the formation of multiple autoantibodies. For example, antinuclear, antierythrocyte, and antilymphocyte antibodies are produced during the chronic graft-versus-host reaction. In addition, true autoimmune diseases, including autoimmune hemolytic anemia and immune complex–mediated glomerulonephritis, can be induced in this manner. While such diffuse activation of helper T cell activity clearly can cause autoimmunity, nonspecific stimulation of B lymphocytes can also lead to the production of autoantibodies. T us, the administration of polyclonal B cell activators, such as bacterial endotoxin, to normal mice leads to the production of a number of autoantibodies, including those to DNA and IgG (rheumatoid factor). A variety of genetic modifications resulting in hyperresponsiveness of B cells also can lead to the production of autoantibodies and, in animals of appropriate genetic background, a lupus-like syndrome. Moreover, excess B cell activating factor (BAFF), a B cell survival factor, can cause T cell–independent B cell activation and the development of autoimmunity. SLE can also be induced in mice through exuberant dendritic cell activation, through a redundancy of TLR7 on the Y chromosome (as in BXSB-Yaa mice), or through exposure to CpG, a ligand for TLR9. T e ensuing induction of inflammatory mediators can cause a switch from the production of nonpathogenic IgM autoantibodies to the production of pathogenic IgG autoantibodies in the absence of antigen-specific T cell help. Aberrant selection of the B or T cell repertoire at the time of antigen receptor expression can also predispose to autoimmunity. For example, B cell immunodeficiency caused by an absence of the B cell receptor–associated kinase (Bruton's tyrosine kinase) leads to X-linked agammaglobulinemia. T is syndrome is characterized by reduced B cell numbers. T is leads to high levels of BAFF which alter B cell selection and lead to greater survival of autoreactive B cells. Likewise, negative selection of autoreactive T cells in the thymus requires expression of the autoimmune regulator (AIRE) gene that enables the expression of tissue-specific proteins in thymic medullary epithelial cells. Peptides from these proteins are expressed in the context of major histocompatibility complex (MHC) molecules and mediate the central deletion of autoreactive T cells. T e absence of AIRE gene expression leads to a failure of negative selection of autoreactive cells, autoantibody production, and severe inflammatory destruction of multiple organs. Individuals deficient in AIRE gene expression develop autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED).

Primary alterations in the activity of T and/or B cells, cytokine imbalances, or defective immunoregulatory circuits may also contribute to the emergence of autoimmunity. Diminished production of tumor necrosis factor (TNF) and interleukin (IL) 10 has been reported to be associated with the development of autoimmunity. Overproduction or therapeutic administration of type 1 interferon has also been associated with autoimmunity. Overexpression of costimulatory molecules on T cells similarly can lead to autoantibody production.

Autoimmunity may also result from an abnormality of immunoregulatory mechanisms. Observations made in both human autoimmune disease and animal models suggest that defects in the generation and expression of regulatory T cell (Treg) activity may allow the production of autoimmunity. It has recently been appreciated that the IPEX (immunodysregulation, polyendocrinopathy, enteropathy X-linked) syndrome results from the failure to express the FOXP3 gene, which encodes a molecule critical in the differentiation of Tregs. Administration of normal Tregs or of factors derived from them can prevent the development of autoimmune disease in rodent models of autoimmunity, and allogeneic stem cell transplantation ameliorates human IPEX. Abnormalities in the function of Tregs have been noted in a number of human autoimmune diseases, including rheumatoid arthritis and SLE, although it remains uncertain whether these functional abnormalities are causative or are secondary to inflammation. One of the mechanisms by which Tregs control immune/inflammatory responses is by the production of the cytokine IL-10. In this regard, children with a deficiency in the expression of IL-10 or the IL-10 receptor develop inflammatory bowel disease that mimics Crohn's disease and that can be cured by allogeneic stem cell transplantation. Finally, recent data indicate that B cells may also exert regulatory function, largely through the production of IL-10. Deficiency of IL-10-producing regulatory B cells can prolong the course of multiple sclerosis in an animal model, and such cells are thought to be functionally diminished in human SLE.

It should be apparent that no single mechanism can explain all the varied manifestations of autoimmunity or autoimmune disease. Furthermore, genetic evaluation has shown that convergence of a number of abnormalities is often required for the induction of an autoimmune disease. Additional factors that appear to be important determinants in the induction of autoimmunity include age, sex (many autoimmune diseases are far more common in women), exposure to infectious agents, and environmental contacts. How all of these disparate factors affect the capacity to develop self-reactivity is currently being investigated intensively.

GENETIC CONSIDERATIONS



Evidence in humans that there are susceptibility genes for autoimmunity comes from family studies and especially from studies of twins. Studies in type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and SLE have shown that ~15–30% of pairs of monozygotic twins show disease concordance, whereas the figure is <5% for dizygotic twins. T e occurrence of different autoimmune diseases within the same family has suggested that certain susceptibility genes may predispose to a variety of autoimmune diseases. Genome-wide association studies have begun to identify polymorphisms in individual genes that are associated with specific autoimmune diseases. More than 50 genetic polymorphisms associated with one or more autoimmune diseases have been identified to date. It is notable that some genes are associated with multiple autoimmune diseases, whereas others are specifically associated with only one autoimmune condition. Moreover, recent genetic evidence suggests that clusters of genetic risk factors can commonly be found in groups of autoimmune diseases. Four general clusters have been identified: one group of 6 genetic polymorphisms most frequently associated with Crohn's disease, psoriasis, and multiple sclerosis; a second cluster of 8 polymorphisms most strongly associated with celiac disease, rheumatoid arthritis, and SLE; a third cluster of 7 polymorphisms most strongly associated with type 1 diabetes, multiple sclerosis, and rheumatoid arthritis; and a fourth cluster of more than 12 polymorphisms most strongly associated with type 1 diabetes, rheumatoid arthritis, celiac disease, Crohn's disease, and SLE. T ese results imply that autoimmune diseases with widely different clinical presentations and patterns of organ involvement could involve similar immunopathogenic pathways. For example, the same allele of the gene encoding PTPN22 is associated with multiple autoimmune diseases. Its product is a phosphatase expressed by a variety of hematopoietic cells that downregulates antigen receptor–mediated stimulation of T and B cells. T e risk allele is associated with type 1 diabetes mellitus, rheumatoid arthritis, and SLE in some populations. T e explanation for the association of this polymorphism with autoimmune disease is uncertain, but it is likely that it diminishes antigen receptor signaling during lymphocyte development, permitting escape of autoreactive clones or decreased activation-induced apoptosis of autoantigen-reactive lymphocytes in the periphery. In recent years, genome-wide association studies have demonstrated a variety of other genes that are involved in human autoimmune diseases. Most genes individually confer a relatively low risk for autoimmune diseases and are found in normal individuals. No gene

has been identified that is essential for autoimmune diseases. In addition to this evidence from humans, certain inbred mouse strains reproducibly develop specific spontaneous or experimentally induced autoimmune diseases, whereas others do not. T ese findings have led to an extensive search for genes that determine susceptibility to autoimmune disease and for genes that might be protective.

T e strongest consistent association for susceptibility to autoimmune disease is with particular MHC alleles. It has been suggested that the association of MHC genotype with autoimmune disease relates to differences in the ability of different allelic variations of MHC molecules to present autoantigenic peptides to autoreactive T cells. An alternative hypothesis involves the role of MHC alleles in shaping the T cell receptor repertoire during T cell ontogeny in the thymus. In addition, specific MHC gene products may themselves be the source of peptides that can be recognized by T cells. Cross-reactivity between such MHC peptides and peptides derived from proteins produced by common microbes may trigger autoimmunity by molecular mimicry. However, MHC genotype alone does not determine the development of autoimmunity. Identical twins are far more likely to develop the same autoimmune disease than MHC-identical nontwin siblings; this observation suggests that genetic factors other than the MHC affect disease susceptibility. Studies of the genetics of type 1 diabetes mellitus, SLE, rheumatoid arthritis, and multiple sclerosis in humans and mice have identified several independently segregating disease susceptibility loci in addition to the MHC. Genes that encode molecules of the innate immune response are also involved in autoimmunity. In humans, inherited homozygous deficiency of the early proteins of the classic pathway of complement (C1q, C4, or C2) as well as genes involved in the type 1 interferon pathway are very strongly associated with the development of SLE.

IMMUNOPATHOGENIC MECHANISMS IN AUTOIMMUNE DISEASES

T e mechanisms of tissue injury in autoimmune diseases can be divided into antibody-mediated and cell-mediated processes. Representative examples are listed in **Table 3-3**.

T e pathogenicity of autoantibodies can be mediated through several mechanisms, including opsonization of soluble factors or cells, activation of an inflammatory cascade via the complement system, and interference with the physiologic function of soluble molecules or cells.

In autoimmune thrombocytopenic purpura, opsonization of platelets targets them for elimination by phagocytes. Likewise, in autoimmune hemolytic anemia, binding of immunoglobulin to red cell membranes leads to phagocytosis and lysis of the opsonized cell. Goodpasture's syndrome (anti-GBM disease), a disease characterized by lung hemorrhage and severe glomerulonephritis, represents an example of antibody binding leading to local activation of complement and neutrophil accumulation and activation. T e autoantibody in

TABLE 3-3

MECHANISMS OF TISSUE DAMAGE IN AUTOIMMUNE DISEASE

EFFECTOR	MECHANISM	TARGET	DISEASE
Autoantibody	Blocking or inactivation	α Chain of the nicotinic acetylcholine receptor	Myasthenia gravis
		Phospholipid–β_2-glycoprotein I complex	Antiphospholipid syndrome
		Insulin receptor	Insulin-resistant diabetes mellitus
		Intrinsic factor	Pernicious anemia
	Stimulation	TSH receptor (LATS)	Graves' disease
		Proteinase-3 (ANCA)	Granulomatosis with polyangiitis
		Epidermal cadherin	Pemphigus vulgaris
		Desmoglein 3	
	Complement activation	α_3 Chain of collagen IV	Goodpasture's syndrome (anti-GBM disease)
	Immune complex formation	Double-stranded DNA	Systemic lupus erythematosus
		Immunoglobulin	Rheumatoid arthritis
	Opsonization	Platelet GpIIb:IIIa	Autoimmune thrombocytopenic purpura
		Rh antigens, I antigen	Autoimmune hemolytic anemia
	Antibody-dependent cellular cytotoxicity	Thyroid peroxidase, thyroglobulin	Hashimoto's thyroiditis
T cells	Cytokine production	?	Rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus
	Cellular cytotoxicity	?	Type 1 diabetes mellitus

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; LATS, long-acting thyroid stimulator; TSH, thyroid-stimulating hormone.

this disease binds to the α_3 chain of type IV collagen in the basement membrane. In SLE, activation of the complement cascade at sites of immunoglobulin deposition in renal glomeruli is considered to be a major mechanism of renal damage. Moreover, the DNA- and RNA-containing immune complexes in SLE activate TLR9 and TLR7, respectively, in dendritic cells and promote a proinflammatory, immunogenic milieu conducive to amplification of the autoimmune response.

Autoantibodies can also interfere with normal physiologic functions of cells or soluble factors. Autoantibodies to hormone receptors can lead to stimulation of cells or to inhibition of cell function through interference with receptor signaling. For example, long-acting thyroid stimulators—autoantibodies that bind to the receptor for thyroid-stimulating hormone (TSH)—are present in Graves' disease and function as agonists, causing the thyroid to respond as if there were an excess of TSH. Alternatively, antibodies to the insulin receptor can cause insulin-resistant diabetes mellitus through receptor blockade. In myasthenia gravis, autoantibodies to the acetylcholine receptor can be detected in 85–90% of patients and are responsible for muscle weakness. T e exact location of the antigenic epitope, the valence and af nity of the antibody, and perhaps other characteristics determine whether activation or blockade results from antibody binding.

Antiphospholipid antibodies are associated with thromboembolic events in primary and secondary antiphospholipid syndrome and have also been associated with fetal wastage. The major antibody is directed to the phospholipid–β_2-glycoprotein I complex and appears to exert a procoagulant effect. In pemphigus vulgaris, autoantibodies bind to desmoglein 3, a component of the epidermal cell desmosome, and play a role in the induction of the disease. These antibodies exert their pathologic effect by disrupting cell–cell junctions through stimulation of the production of epithelial proteases, with consequent blister formation. Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), found in granulomatosis with polyangiitis, is an antibody to an intracellular antigen, the 29-kDa serine protease (proteinase-3). In vitro experiments have shown that IgG anti-c-ANCA causes cellular activation and degranulation of primed neutrophils.

It is important to note that autoantibodies of a given specificity may cause disease only in genetically susceptible hosts, as has been shown in experimental models of myasthenia gravis, SLE, rheumatic fever, and rheumatoid arthritis. Furthermore, once organ damage is initiated, new inflammatory cascades are initiated that can sustain and amplify the autoimmune process. Finally, some autoantibodies seem to be markers for disease but have, as yet, no known pathogenic potential.

AUTOIMMUNE DISEASES

Manifestations of autoimmunity are found in a large number of pathologic conditions. However, their presence does not necessarily imply that the pathologic process is an autoimmune disease. A number of attempts to establish formal criteria for the classification of diseases as autoimmune have been made, but none is universally accepted. One set of criteria is shown in **Table 3-4**; however, this scheme should be viewed merely as a guide in consideration of the problem.

To classify a disease as autoimmune, it is necessary to demonstrate that the immune response to a self-antigen causes the observed pathology. Initially, the detection of antibodies to the affected tissue in the serum of patients suffering from various diseases was taken as evidence that these diseases had an autoimmune basis. However, such autoantibodies are also found when tissue damage is caused by trauma or infection and in these cases are secondary to tissue damage. T us, autoimmunity must be shown to be pathogenic before a disease is categorized as autoimmune.

To confirm autoantibody pathogenicity, it may be possible to transfer disease to experimental animals by the administration of autoantibodies from a patient, with the subsequent development of pathology in the recipient similar to that seen in the patient. T is scenario has been documented, for example, in Graves' disease. Some autoimmune diseases can be transferred from mother to fetus and are observed in the newborn babies of diseased mothers. T e symptoms of the disease in the newborn usually disappear as the levels of maternal antibody decrease. An exception, however, is congenital heart block, in which damage to the developing conducting system of the heart follows in utero transfer of anti-Ro antibody from the mother to the

TABLE 3-4

HUMAN AUTOIMMUNE DISEASE: PRESUMPTIVE EVIDENCE FOR IMMUNOLOGIC PATHOGENESIS

Major Criteria
1. Presence of autoantibodies or evidence of cellular reactivity to self
2. Documentation of relevant autoantibody or lymphocytic infiltrate in the pathologic lesion
3. Demonstration that relevant autoantibody or T cells can cause tissue pathology
a. Transplacental transmission
b. Adaptive transfer into animals
c. In vitro impact on cellular function
Supportive Evidence
1. Reasonable animal model
2. Beneficial ef ect from immunosuppressive agents
3. Association with other evidence of autoimmunity
4. No evidence of infection or other obvious cause

fetus. T is antibody transfer can result in a permanent developmental defect in the heart.

In most situations, the critical factors that determine when the development of autoimmunity results in autoimmune disease have not been delineated. T e relationship of autoimmunity to the development of autoimmune disease may be associated with the fine specificity of the antibodies or T cells or their specific effector capabilities. In many circumstances, a mechanistic understanding of the pathogenic potential of autoantibodies has not been established. In some autoimmune diseases, biased production of cytokines by helper T (T_H) cells may play a role in pathogenesis. In this regard, T cells can differentiate into specialized effector cells that predominantly produce interferon γ (T_H1), IL-4 (T_H2), or IL-17 (T_H17) or that provide help to B cells (T follicular helper, T_{FH}) **(Chap. 1)**. T_H1 cells facilitate macrophage activation and classic cell-mediated immunity, whereas T_H2 cells are thought to have regulatory functions and are involved in the resolution of normal immune responses as well as in the development of responses to a variety of parasites. T_H17 cells produce a number of inflammatory cytokines, including IL-17 and IL-22, and seem to be prominently involved in host resistance to certain fungal infections. T_{FH} cells help B cells by constitutively producing IL-21. In a number of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, and Crohn's disease, there appears to be biased differentiation of T_H1 and T_H17 cells, with resultant organ damage. Studies suggest an accentuated differentiation of T_H17 cells associated with animal models of inflammatory arthritis, whereas increased differentiation of T_{FH} cells has been associated with animal models of SLE.

ORGAN-SPECIFIC VERSUS SYSTEMIC AUTOIMMUNE DISEASES

T e spectrum of autoimmune diseases ranges from conditions specifically affecting a single organ to systemic disorders that involve many organs **(Table 3-5)**. Hashimoto's autoimmune thyroiditis is an example of an organ-specific autoimmune disease. In this disorder, a specific lesion in the thyroid is associated with infiltration of mononuclear cells and damage to follicular cells. Antibody to thyroid constituents can be demonstrated in nearly all cases. Other organ- or tissue-specific autoimmune disorders include pemphigus vulgaris, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, Goodpasture's syndrome, myasthenia gravis, and sympathetic ophthalmia. One important feature of some organ-specific autoimmune diseases is the tendency for overlap, such that an individual with one specific syndrome is more likely to develop a second syndrome. For example, there is a high incidence of pernicious anemia in individuals with autoimmune thyroiditis. More striking is the tendency for individuals with an organ-specific autoimmune disease to develop multiple other manifestations of autoimmunity without the development of associated organ pathology. T us, as many as 50% of individuals with pernicious anemia have non-cross-reacting antibodies to thyroid constituents, whereas patients with myasthenia gravis may develop antinuclear antibodies, antithyroid antibodies, rheumatoid factor, antilymphocyte antibodies, and polyclonal hypergammaglobulinemia. Part of the explanation may relate to the genetic elements shared by individuals with these different diseases.

Systemic autoimmune diseases differ from organ-specific diseases in that pathologic lesions are found in multiple diverse organs and tissues. T e hallmark of these conditions is the demonstration of associated relevant autoimmune manifestations that are likely to have an etiologic role in organ pathology. SLE represents the prototype of these disorders because of its abundant autoimmune manifestations. SLE is a disease of protean manifestations that characteristically involves the kidneys, joints, skin, serosal surfaces, blood vessels, and central nervous system. T e disease is associated with a vast array of autoantibodies whose production appears to be a part of a generalized hyperreactivity of the humoral

TABLE 3-5

DISEASES ON THE AUTOIMMUNE SPECTRUM

Organ Specif c	
Graves' disease	Vitiligo
Hashimoto's thyroiditis	Autoimmune hemolytic anemia
Autoimmune polyglandular syndrome	Autoimmune thrombocytopenic purpura
Type 1 diabetes mellitus	Pernicious anemia
Insulin-resistant diabetes mellitus	Myasthenia gravis
Immune-mediated infertility	Multiple sclerosis
Autoimmune Addison's disease	Guillain-Barré syndrome
Pemphigus vulgaris	Stif -person syndrome
Pemphigus foliaceus	Acute rheumatic fever
Dermatitis herpetiformis	Sympathetic ophthalmia
Autoimmune alopecia	Goodpasture's syndrome
Organ Nonspecif c (Systemic)	
Systemic lupus erythematosus	Granulomatosis with polyangiitis
Rheumatoid arthritis	Antiphospholipid syndrome
Systemic necrotizing vasculitis	Sjögren's syndrome

immune system. Other features of SLE include generalized B cell hyperresponsiveness and polyclonal hypergammaglobulinemia. Current evidence suggests that both hypo- and hyperresponsiveness to antigen can lead to survival and activation of autoreactive B cells in SLE. T e autoantibodies in SLE are thought to arise as part of an accentuated T cell–dependent B cell response since most pathogenic anti-DNA autoantibodies exhibit evidence of extensive somatic hypermutation.

TREATMENT Autoimmune Diseases

Treatment of autoimmune diseases can focus on suppressing the induction of autoimmunity, restoring normal regulatory mechanisms, or inhibiting the effector mechanisms. To decrease the number or function of autoreactive cells, immunosuppressive or ablative therapies are most commonly used. In recent years, cytokine blockade has been demonstrated to be effective in preventing immune activation in some diseases or in inhibiting the extensive inflammatory effector mechanisms characteristic of these diseases. New therapies have also been developed to target lymphoid cells more specifically by blocking a costimulatory signal needed for T or B cell activation, by blocking the migratory capacity of lymphocytes, or by eliminating the effector T cells or B cells. T e ef cacy of these therapies in some diseases—e.g., SLE (belimumab), rheumatoid arthritis (TNF neutralization, IL-6 receptor blockade, CD28 competition, B cell depletion, IL-1 competition), psoriasis (IL-12/23 depletion, TNF neutralization), and inflammatory bowel disease (TNF neutralization, IL-12 neutralization)—has been demonstrated. One major advance in inhibiting effector mechanisms has been the introduction of cytokine blockade that appears to limit organ damage in some diseases, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and the spondyloarthritides. Small molecules that block cytokine signaling pathways have recently been introduced into the clinic. Biologicals that interface with T cell activation (CTLA-4Ig) or delete B cells (anti-CD20 antibody) have recently been approved for the treatment of rheumatoid arthritis. T erapies that prevent target-organ damage or support target-organ function remain important in the management of autoimmune disease.

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SECTION II

DISORDERS OF IMMUNE-MEDIATED INJURY

CHAPTER 4

SYSTEMIC LUPUS ERYTHEMATOSUS

Bevra Hannahs Hahn

DEFINITION AND PREVALENCE

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes. In most patients, autoantibodies are present for a few years before the first clinical symptom appears. Ninety percent of patients are women of child-bearing years; people of all genders, ages, and ethnic groups are susceptible. Prevalence of SLE in the United States is 20 to 150 per 100,000 women depending on race and gender; highest prevalence is in African-American and Afro-Caribbean women, and lowest prevalence is in white men.

PATHOGENESIS AND ETIOLOGY

T e proposed pathogenic mechanisms of SLE are illustrated in **Fig. 4-1**. Interactions between susceptibility genes and environmental factors result in abnormal immune responses, which vary between different patients. T ose responses may include (1) activation of innate immunity (dendritic cells, monocyte/macrophages) by CpG DNA, DNA in immune complexes, viral DNA or RNA, and RNA in RNA/protein self-antigens; (2) lowered activation thresholds and abnormal activation pathways in adaptive immunity cells (mature T and B lymphocytes); (3) ineffective regulatory CD4+ and CD8+ T cells, B cells, and myeloid-derived suppressor cells; and (4) reduced clearance of immune complexes and apoptotic cells. Self-antigens (nucleosomal DNA/protein; RNA/protein in Sm, Ro, and La; phospholipids) are recognized by the immune system in surface blebs of apoptotic cells; thus autoantigens, autoantibodies, and immune complexes persist for prolonged periods of time, allowing inflammation and disease to develop. Immune cell activation is accompanied by increased secretion of proinflammatory type 1 and 2 interferons (IFNs), tumor necrosis factor α (TNF-α), interleukin (IL) 17 and B cell-maturation/survival cytokines B lymphocyte stimulator (BLyS/BAFF), and IL-10. Upregulation of genes induced by IFNs is a genetic "signature" in peripheral blood cells of 50–60% of SLE patients. Decreased production of other cytokines also contributes to SLE: lupus T and natural killer (NK) cells fail to produce enough IL-2 and transforming growth factor beta (TGF-β) to induce and sustain regulatory CD4+ and CD8+ T cells. T e result of these abnormalities is sustained production of autoantibodies (referred to in Fig. 4-1 and described in **Table 4-1**) and immune complexes; pathogenic subsets bind target tissues, with activation of complement, leading to release of cytokines, chemokines, vasoactive peptides, oxidants, and proteolytic enzymes. T is results in activation of multiple tissue cells (endothelial cells, tissue-fixed macrophages, mesangial cells, podocytes, renal tubular epithelial cells) and influx into target tissues of T and B cells, monocyte/macrophages, and dendritic cells. In the setting of chronic inflammation, accumulation of growth factors and products of chronic oxidation contribute to irreversible tissue damage, including fibrosis/sclerosis in glomeruli, arteries, lungs, and other tissues.

SLE is a multigenic disease. Rare single-gene defects confer high hazard ratios (HRs) for SLE (5 to 25), including homozygous deficiencies of early components of complement (C1q,r,s; C2; C4) and a mutation in TREX1 on the X chromosome. In most genetically susceptible individuals, normal alleles of multiple genes each contribute a small amount to abnormal immune/inflammation/tissue damage responses; if enough predisposing variations are present, disease results. Approximately 45 predisposing genes (examples listed in Fig. 4-1)have been identified in recent genome-wide association studies in different racial groups. Individually, they confer an HR for SLE of 1.5–3 and account for approximately 18% of disease susceptibility, suggesting

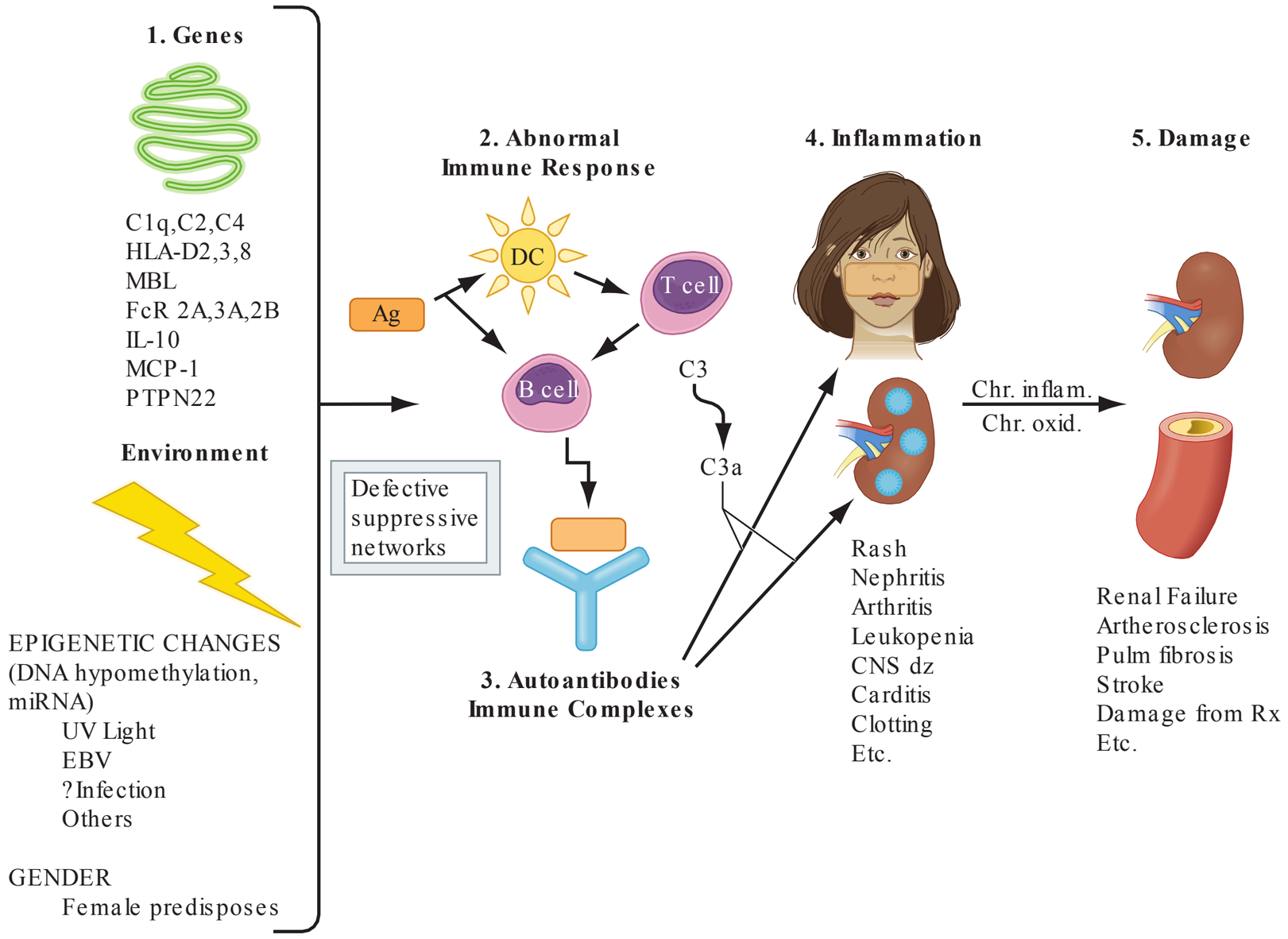


FIGURE 4-1

Pathogenesis of systemic lupus erythematosus (SLE). Genes confirmed in more than one genome-wide association analysis in northern European whites (several confirmed in Asians as well) as increasing susceptibility to SLE or lupus nephritis are listed (reviewed in SG Guerra et al: Arthritis Res Ther 14:211, 2012). Gene-environment interactions (reviewed in KH Costenbader et al: Autoimmune Rev 11:604, 2012) result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, cause inflammation, and over time lead to irreversible organ damage (reviewed in GC Tsokos: N Engl J Med 365:2110, 2011; and BH Hahn, in DJ Wallace, BH Hahn [eds]: Dubois' Lupus Erythematosus and Related Syndromes, 8th ed. New York, Elsevier, 2013). Ag, antigen; C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemotactic protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

that environmental exposures and epigenetics play major roles. Predisposing, antigen-presenting human leukocyte antigen (HLA) molecules are most commonly found, in multiple ethnic groups (HLA DRB1 *0301 and *1501, as well as multiple genes across the major histocompatibility complex (MHC) 120-gene region). Other genetic factors in whites include innate immunity pathway gene polymorphisms, especially associated with IFN-α (STAT4, IRF5, IRAK1, TNFAIP3, PTPN22), genes in lymphocyte signaling pathways (PTPN22, PDCD-1, Ox40L, BANK-1, LYN, BLK), genes that affect clearance of apoptotic cells or immune complexes (C1q, FCRGIIA, FCRGIIIA, CRP, ITGAM), genes that influence neutrophil adherence (ITGAM), and genes that influence DNA repair (TREX-1). Some polymorphisms influence clinical manifestations; such as single nucleotide polymorphisms (SNPs) of STAT4 that associate with severe disease, anti-DNA, nephritis, and antiphospholipid syndrome, and an allele of FCGRIIA encoding a receptor that binds immune complexes poorly and predisposes to nephritis. Some gene effects are in promoter regions (e.g., IL-10), and others are conferred by copy numbers (e.g., C4A). In addition to genome-encoded susceptibility and protective genes, the influence of certain microRNAs (miRNAs) on gene transcription, as well as posttranscriptional epigenetic modification of DNA (which is hypomethylated in T cells of SLE patients), probably play major roles in disease susceptibility.

Some gene polymorphisms contribute to several autoimmune diseases, such as STAT4 and CTLA4. All of these gene polymorphisms/transcription/epigenetic combinations influence immune responses to the external and internal environment; when such responses are too high and/or too prolonged and/or inadequately regulated, autoimmune disease results.

Female sex is permissive for SLE with evidence for hormone effects, genes on the X chromosome, and epigenetic differences between genders playing a role. Females of many mammalian species make higher

TABLE 4-1

AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

ANTIBODY	PREVALENCE, %	ANTIGEN RECOGNIZED	CLINICAL UTILITY
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests make SLE unlikely
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNA	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites
Anti-Ro (SS-A)	30	Protein complexed to hYRNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus, and to neonatal lupus with congenital heart block; associated with decreased risk for nephritis
Anti-La (SS-B)	10	47-kDa protein complexed to hYRNA	Usually associated with anti-Ro; associated with decreased risk for nephritis
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE
Antiphospholipid	50	Phospholipids, β_2 glycoprotein 1 (β_2G1) cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β_2G1, sensitive prothrombin time (DRVVT); predisposes to clotting, fetal loss, thrombocytopenia
Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs test; a small proportion develops overt hemolysis
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia, but sensitivity and specificity are not good; this is not a useful clinical test
Antineuronal (includes antiglutamate receptor)	60	Neuronal and lymphocyte surface antigens	In some series, a positive test in CSF correlates with active CNS lupus
Antiribosomal P	20	Protein in ribosomes	In some series, a positive test in serum correlates with depression or psychosis due to CNS lupus

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DRVVT, dilute Russell viper venom time; ELISA, enzyme-linked immunosorbent assay.

antibody responses than males. Women exposed to estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE (1.2- to 2-fold). Estradiol binds to receptors on T and B lymphocytes, increasing activation and survival of those cells, thus favoring prolonged immune responses. Genes on the X chromosome that influence SLE, such as TREX-1, may play a role in gender predisposition, possibly because some genes on the second X in females are not silent. People with XXY karyotype (Klinefelter's syndrome) have a significantly increased risk for SLE.

Several environmental stimuli may influence SLE (Fig. 4-1). Exposure to ultraviolet light causes flares of SLE in approximately 70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic. Some infections induce normal immune responses that involve certain T and B cells that recognize self-antigens; such cells are not appropriately regulated, and autoantibody production occurs. Most SLE patients have autoantibodies for 3 years or more before the first symptoms of disease, suggesting that regulation controls the degree of autoimmunity for years before quantities and qualities of autoantibodies and pathogenic B and T cells cause clinical disease. Epstein-Barr virus (EBV) may be one infectious agent that can trigger SLE in susceptible individuals. Children and adults with SLE are more likely to be infected by EBV than age-, sex-, and ethnicity-matched controls. EBV contains amino acid sequences that mimic sequences on human spliceosomes (RNA/protein antigens) often recognized by autoantibodies in people with SLE. Current tobacco smoking increases risk for SLE (odds ratio [OR] 1.5). Prolonged occupational exposure to silica (e.g., inhalation of soap powder dust or soil in farming activities) increases risk (OR 4.3) in African-American women.

T us, interplay between genetic susceptibility, environment, gender, and abnormal immune responses results in autoimmunity **(Chap. 3)**.

PATHOLOGY

In SLE, biopsies of affected skin show deposition of Ig at the dermal-epidermal junction (DEJ), injury to basal keratinocytes, and inflammation dominated by T lymphocytes in the DEJ and around blood vessels and dermal appendages. Clinically unaffected skin may also show Ig deposition at the DEJ.

In renal biopsies, the pattern and severity of injury are important in diagnosis and in selecting the best therapy. Most recent clinical studies of lupus nephritis have used the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) classification **(Table 4-2)**. In the ISN/RPS classification, the addition of "a" for active and "c" for chronic changes gives physicians information regarding the potential reversibility of disease. T e system focuses on glomerular disease, although the presence of tubular interstitial and vascular disease is important to clinical outcomes. In general, class III and IV disease, as well as class V accompanied by III or IV disease, should be treated with aggressive immunosuppression if possible, because there is a high risk for end-stage renal disease (ESRD) if patients are untreated or undertreated. In contrast, treatment for lupus nephritis is not recommended in patients with class I or II disease or with extensive irreversible changes. In the recent Systemic Lupus International Collaborating Clinic (SLICC) criteria for classification of SLE, a diagnosis

TABLE 4-2

CLASSIFICATION OF LUPUS NEPHRITIS (INTERNATIONAL SOCIETY OF NEPHROLOGY AND RENAL PATHOLOGY SOCIETY)
Class I: Minimal Mesangial Lupus Nephritis
Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
Class II: Mesangial Proliferative Lupus Nephritis
Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
Class III: Focal Lupus Nephritis
Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving ≤50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations. Class III (A): Active lesions—focal proliferative lupus nephritis Class III (A/C): Active and chronic lesions—focal proliferative and sclerosing lupus nephritis Class III (C): Chronic inactive lesions with glomerular scars—focal sclerosing lupus nephritis
Class IV: Diffuse Lupus Nephritis
Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than one-half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation. Class IV-S (A): Active lesions—diffuse segmental proliferative lupus nephritis Class IV-G (A): Active lesions—diffuse global proliferative lupus nephritis Class IV-S (A/C): Active and chronic lesions—diffuse segmental proliferative and sclerosing lupus nephritis Class IV-G (A/C): Active and chronic lesions—diffuse global proliferative and sclerosing lupus nephritis Class IV-S (C): Chronic inactive lesions with scars—diffuse segmental sclerosing lupus nephritis Class IV-G (C): Chronic inactive lesions with scars—diffuse global sclerosing lupus nephritis
Class V: Membranous Lupus Nephritis
Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis.
Class VI: Advanced Sclerotic Lupus Nephritis
≥90% of glomeruli globally sclerosed without residual activity.

Note: Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, and severity of arteriosclerosis or other vascular lesions.

Source: JJ Weening et al: Kidney Int 65:521, 2004. Reprinted by permission from Macmillan Publishers Ltd., Copyright 2004.

TABLE 4-3

SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINIC CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

CLINICAL MANIFESTATIONS	IMMUNOLOGIC MANIFESTATIONS
Skin	ANA > reference negative value
Acute, subacute cutaneous LE	Anti-dsDNA
Chronic cutaneous LE	Anti-Sm
Oral ulcers	Antiphospholipid
Alopecia	Low serum complement
Synovitis	Positive direct Coombs test
Serositis	
Renal	
Prot/Cr ≥0.5	
RBC casts	
Biopsy[a]	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000) or Lymphopenia (<1000)	
Thrombocytopenia (<100,000)	

[a]Renal biopsy read as systemic lupus qualifies for classification as SLE even if none of the other above features are present.

Interpretation: Presence of any 4 criteria (must have at least 1 in each category) qualifies patient to be classified as having SLE with 93% specificity and 92% sensitivity.

Abbreviations: ANA, antinuclear antibody; Cr, creatinine; LE, lupus erythematosus; Prot, protein.

Source: M Petri et al: Arthritis Rheum 64:2677, 2012. Because these criteria are new, currently ongoing clinical studies use prior American College of Rheumatology Criteria; see EM Tan et al: Arthritis Rheum 25:1271, 1982; update MC Hochberg: Arthritis Rheum 40:1725, 1997.

can be established on the basis of renal histology without meeting additional criteria **(Table 4-3)**.

Histologic abnormalities in blood vessels may also determine therapy. Patterns of vasculitis are not specific for SLE but may indicate active disease: leukocytoclastic vasculitis is most common **(Chap. 11)**.

Lymph node biopsies are usually performed to rule out infection or malignancies. In SLE, they show nonspecific diffuse chronic inflammation.

DIAGNOSIS

The diagnosis of SLE is based on characteristic clinical features and autoantibodies. Current criteria for classification are listed in Table 4-3, and an algorithm for diagnosis and initial therapy is shown in **Fig. 4-2**. The criteria are intended for confirming the diagnosis of SLE in patients included in studies; the author uses them in individual patients for estimating the probability that a disease is SLE. Any combination of four or more criteria, with at least one in the clinical and one in the immunologic category, well documented at any time during an individual's history, makes it likely that the patient has SLE. (Specificity and sensitivity are ~93% and ~92%, respectively.) In many patients, criteria accrue over time. Antinuclear antibodies (ANA) are positive in >98% of patients during the course of disease; repeated negative tests by immunofluorescent methods suggest that the diagnosis is not SLE, unless other autoantibodies are present (Fig. 4-2). High-titer IgG antibodies to double-stranded DNA and antibodies to the Sm antigen are both specific for SLE and, therefore, favor the diagnosis in the presence of compatible clinical manifestations. The presence in an individual of multiple autoantibodies without clinical symptoms should not be considered diagnostic for SLE, although such persons are at increased risk.

INTERPRETATION OF CLINICAL MANIFESTATIONS

When a diagnosis of SLE is made, it is important to establish the severity and potential reversibility of the illness and to estimate the possible consequences of various therapeutic interventions. In the following paragraphs, descriptions of some disease manifestations begin with relatively mild problems and progress to those more life-threatening.

OVERVIEW AND SYSTEMIC MANIFESTATIONS

At its onset, SLE may involve one or several organ systems; over time, additional manifestations may occur (Tables 4-3 and **4-4**). Most of the autoantibodies characteristic of each person are present at thetime clinical manifestations appear (Tables 4-1 and 4-3). Severity of SLE varies from mild and intermittent to severe and fulminant. Approximately 85% of patients have either continuing active disease (while being treated) or one or more flares of active disease annually. Permanent complete remissions (absence of symptoms with no treatment) are rare. Systemic symptoms, particularly fatigue and myalgias/arthralgias, are present most of the time. Severe systemic illness requiring glucocorticoid therapy can occur with fever, prostration, weight loss, and anemia with or without other organ-targeted manifestations.

MUSCULOSKELETAL MANIFESTATIONS

Most people with SLE have intermittent polyarthritis, varying from mild to disabling, characterized by soft tissue swelling and tenderness in joints and/or tendons, most commonly in hands, wrists, and knees. Joint deformities (hands and feet) develop in only 10%. Erosions on

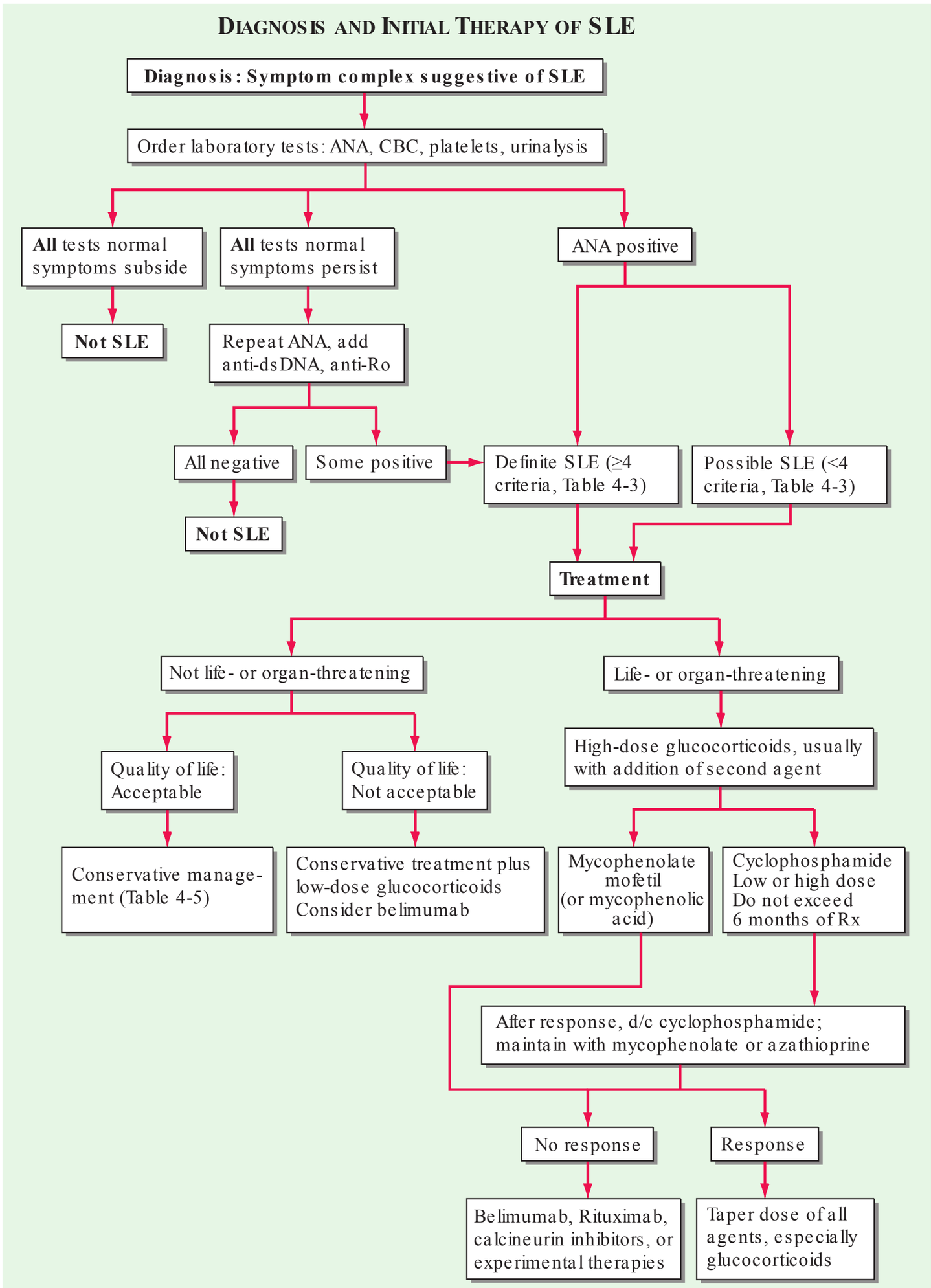


FIGURE 4-2

Algorithm for diagnosis and initial therapy of systemic lupus erythematosus (SLE). For guidelines on management of lupus and lupus nephritis, see BH Hahn et al: Arthritis Care Res (Hoboken) 64:797, 2012; GK Bertsias et al: Ann Rheum Dis 71:1771, 2012; and G Bertsias et al: Ann Rheum Dis 67:195, 2008. For details on mycophenolate and cyclophosphamide induction and maintenance therapies, see L Henderson et al: Cochrane Database Syst Rev 12:CD002922, 2012; Z Touma et al: J Rheumatol 38:69, 2011; EM Ginzler et al: Arthritis Rheum 62:211, 2010; FA Houssiau et al: Ann Rheum Dis 69:61, 2010; and MA Dooley et al: N Engl J Med 365:1886, 2011. For belimumab in treatment, see BH Hahn: N Eng J Med 368:1528, 2013. For rituximab, see L Lightstone: Lupus 22:390, 2013; and BH Rovin et al: Arthritis Rheum 64:1215, 2012. ANA, antinuclear antibodies; CBC, complete blood count.

joint x-rays are rare but can be identified by ultrasound in almost half of patients. Some individuals have rheumatoid-like arthritis with erosions and fulfill criteria for both RA and SLE ("rhupus"); they may be coded as having both diseases. If pain persists in a single joint, such as knee, shoulder, or hip, a diagnosis of ischemic necrosis of bone should be considered, particularly if there are no other manifestations of active SLE because its prevalence is increased in SLE, especially in patients treated with systemic glucocorticoids. Myositis with clinical muscle weakness, elevated creatine kinase levels, positive magnetic resonance imaging (MRI) scan, and muscle necrosis and inflammation on biopsy can occur, although most patients have myalgias without frank myositis.

TABLE 4-4

CLINICAL MANIFESTATIONS OF SLE AND PREVALENCE OVER THE ENTIRE COURSE OF DISEASE[a]

MANIFESTATION	PREVALENCE, %
Systemic: Fatigue, malaise, fever, anorexia, weight loss	95
Musculoskeletal	95
Arthralgias/myalgias	95
Nonerosive polyarthritis	60
Hand deformities	10
Myopathy/myositis	25/5
Ischemic necrosis of bone	15
Cutaneous	80
Photosensitivity	70
Malar rash	50
Oral ulcers	40
Alopecia	40
Discoid rash	20
Vasculitis rash	20
Other (e.g., urticaria, subacute cutaneous lupus)	15
Hematologic	85
Anemia (chronic disease)	70
Leukopenia (<4000/μL)	65
Lymphopenia (<1500/μL)	50
Thrombocytopenia (<100,000/μL)	15
Lymphadenopathy	15
Splenomegaly	15
Hemolytic anemia	10
Neurologic	60
Cognitive disorder	50
Mood disorder	40
Headache	25
Seizures	20
Mono-, polyneuropathy	15
Stroke, TIA	10
Acute confusional state or movement disorder	2–5
Aseptic meningitis, myelopathy	<1
Cardiopulmonary	60
Pleurisy, pericarditis, effusions	30–50
Myocarditis, endocarditis	10
Lupus pneumonitis	10
Coronary artery disease	10
Interstitial fibrosis	5
Pulmonary hypertension, ARDS, hemorrhage	<5
Shrinking lung syndrome	<5
Renal	30–50
Proteinuria ≥500 mg/24 h, cellular casts	30–50
Nephrotic syndrome	25
End-stage renal disease	5–10
Gastrointestinal	40
Nonspecific (nausea, mild pain, diarrhea)	30
Abnormal liver enzymes	40
Vasculitis	5
Thrombosis	15
Venous	10
Arterial	5
Ocular	15
Sicca syndrome	15
Conjunctivitis, episcleritis	10
Vasculitis	5

[a]Numbers indicate percentage of patients who have the manifestation at some time during the course of illness.

Abbreviations: ARDS, acute respiratory distress syndrome; TIA, transient ischemic attack.

Glucocorticoid therapies (commonly) and antimalarial therapies (rarely) can cause muscle weakness; these adverse effects must be distinguished from active inflammatory disease.

CUTANEOUS MANIFESTATIONS

Lupus dermatitis can be classified as acute, subacute, or chronic, and there are many different types of lesions encompassed within these groups. Discoid lupus erythematosus (DLE) is the most common chronic dermatitis in lupus; lesions are roughly circular with slightly raised, scaly hyperpigmented erythematous rims and depigmented, atrophic centers in which all dermal appendages are permanently destroyed. Lesions can be disfiguring, particularly on the face and scalp. Treatment consists primarily of topical or locally injected glucocorticoids and systemic antimalarials. Only 5% of people with DLE have SLE (although half have positive ANA); however, among individuals with SLE, as many as 20% have DLE. The most common acute SLE rash is a photosensitive, slightly raised erythema, occasionally scaly, on the face (particularly the cheeks and nose—the "butterfly" rash), ears, chin, V region of the neck and chest, upper back, and extensor surfaces of the arms. Worsening of this rash often accompanies flare of systemic disease. Subacute cutaneous lupus erythematosus (SCLE) consists of scaly red patches similar to psoriasis, or circular flat red-rimmed lesions. Patients with these manifestations are exquisitely photosensitive; most have antibodies to Ro (SS-A). Other SLE rashes include recurring urticaria, lichen planus-like dermatitis, bullae, and panniculitis ("lupus profundus"). Rashes can be minor or severe; they may be the major disease manifestation. Small ulcerations on the oral or nasal mucosa are common in SLE; the lesions resemble aphthous ulcers.

RENAL MANIFESTATIONS

Nephritis is usually the most serious manifestation of SLE, particularly because nephritis and infection are the leading causes of mortality in the first decade of disease. Because nephritis is asymptomatic in most lupus patients, urinalysis should be ordered in any person suspected of having SLE. T e classification of lupus nephritis is primarily histologic (see "Pathology," above, and Table 4-2). Renal biopsy is recommended for every SLE patient with any clinical evidence of nephritis; results are used to plan current and near-future therapies. Patients with dangerous proliferative forms of glomerular damage (ISN III and IV) usually have microscopic hematuria and proteinuria (>500 mg per 24 h); approximately one-half develop nephrotic syndrome, and most develop hypertension. If diffuse proliferative glomerulonephritis (DPGN) is inadequately treated, virtually all patients develop ESRD within 2 years of diagnosis. T erefore, aggressive immunosuppression is indicated (usually systemic glucocorticoids plus a cytotoxic drug), unless damage is irreversible (Fig. 4-2, **Table 4-5**). African Americans are more likely to develop ESRD than are whites, even with the most current therapies. Overall in the United States, ~20% of individuals with lupus DPGN die or develop ESRD within 10 years of diagnosis. Such individuals require aggressive control of SLE and of the complications of renal disease and of therapy. Approximately 20% of SLE patients with proteinuria (usually nephrotic) have membranous glomerular changes without proliferative changes on renal biopsy. T eir outcome is better than for those with DPGN, but patients with class V and nephrotic range proteinuria should be treated in the same way as those with classes III or IV proliferative disease. Lupus nephritis tends to be an ongoing disease, with flares requiring re-treatment or increased treatment over many years. For most people with lupus nephritis, accelerated atherosclerosis becomes important after several years of disease; attention must be given to control of systemic inflammation, blood pressure, hyperlipidemia, and hyperglycemia.

NERVOUS SYSTEM MANIFESTATIONS

T ere are many central nervous system (CNS) and peripheral nervous system manifestations of SLE; in some patients, these are the major cause of morbidity and mortality. It is useful to approach this diagnostically by asking first whether the symptoms result from SLE or another condition (such as infection in immunosuppressed individuals or side effects of therapies). If symptoms are related to SLE, it should be determined whether they are caused by a diffuse process (requiring immunosuppression) or vascular occlusive disease (requiring anticoagulation). T e most common manifestation of diffuse CNS lupus is cognitive dysfunction, including dif culties with memory and reasoning. Headaches are also common. When excruciating, they often indicate SLE flare; when milder, they are dif cult to distinguish from migraine or tension headaches. Seizures of any type may be caused by lupus; treatment often requires both antiseizure and immunosuppressive therapies. Psychosis can be the dominant manifestation of SLE; it must be distinguished from glucocorticoid-induced psychosis. T e latter usually occurs in the first weeks of glucocorticoid therapy, at daily doses of ≥40 mg of prednisone or equivalent; psychosis resolves over several days after glucocorticoids are decreased or stopped. Myelopathy is not rare and is often disabling; rapid initiation of immunosuppressive therapy starting with high-dose glucocorticoids is standard of care.

VASCULAR OCCLUSIONS

T e prevalence of transient ischemic attacks, strokes, and myocardial infarctions is increased in patients with SLE. T ese vascular events are increased in, but not exclusive to, SLE patients with antibodies to phospholipids (antiphospholipid antibodies), which are associated with hypercoagulability and acute thrombotic events. Chronic SLE with or without antiphospholipid antibodies is associated with accelerated atherosclerosis. Ischemia in the brain can be caused by focal occlusion (either noninflammatory or associated with vasculitis) or by embolization from carotid artery plaque or from fibrinous vegetations of Libman-Sacks endocarditis. Appropriate tests for antiphospholipid antibodies (see below) and for sources of emboli should be ordered in such patients to estimate the need for, intensity of, and duration of anti-inflammatory and/or anticoagulant therapies. In SLE, myocardial infarctions are primarily manifestations of accelerated atherosclerosis. T e increased risk for vascular events is three- to tenfold overall, and is highest in women <49 years old. Characteristics associated with increased risk for atherosclerosis include older age, hypertension, dyslipidemia, dysfunctional proinflammatory high-density lipoproteins, repeated high scores for disease activity, high cumulative or daily doses of glucocorticoids, and high levels of homocysteine. When it is most likely that an event results from clotting, long-term anticoagulation is the therapy of choice. Two processes can occur at once—vasculitis plus bland vascular occlusions—in which case it is appropriate to treat with anticoagulation plus immunosuppression. Statin therapies reduce levels of low-density lipoproteins (LDL) in SLE patients; reduction of cardiac events by statins has been shown in SLE patients with renal transplants but not in other SLE cohorts to date.

TABLE 4-5

MEDICATIONS FOR THE MANAGEMENT OF SLE

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
NSAIDs, salicylates (Ecotrin[a] and St. Joseph's aspirin[a] approved by FDA for use in SLE)	Doses toward upper limit of recommended range usually required	A2R/ACE inhibitors, glucocorticoids, fluconazole, methotrexate, thiazides	NSAIDs: Higher incidence of aseptic meningitis, elevated liver enzymes, decreased renal function, vasculitis of skin; entire class, especially COX-2-specific inhibitors, may increase risk for myocardial infarction Salicylates: ototoxicity, tinnitus Both: GI events and symptoms, allergic reactions, dermatitis, dizziness, acute renal failure, edema, hypertension
Topical glucocorticoids	Mid potency for face; mid to high potency for other areas	None known	Atrophy of skin, contact dermatitis, folliculitis, hypopigmentation, infection
Topical sunscreens	SPF 15 at least; 30+ preferred	None known	Contact dermatitis
Hydroxychloroquine[a] (quinacrine can be added or substituted)	200–400 mg qd (100 mg qd)	None known	Retinal damage, agranulocytosis, aplastic anemia, ataxia, cardiomyopathy, dizziness, myopathy, ototoxicity, peripheral neuropathy, pigmentation of skin, seizures, thrombocytopenia. Quinacrine usually causes diffuse yellow skin coloration.
DHEA (dehydroepiandrosterone)	200 mg qd	Unclear	Acne, menstrual irregularities, high serum levels of testosterone
Methotrexate (for dermatitis, arthritis)	10–25 mg once a week, PO or SC, with folic acid; decrease dose if CrCl <60 mL/min	Acitretin, leflunomide, NSAIDs and salicylates, penicillins, probenecid, sulfonamides, trimethoprim	Anemia, bone marrow suppression, leukopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, infections, neurotoxicity, pulmonary fibrosis, pneumonitis, severe dermatitis, seizures
Glucocorticoids, oral[a] (several specific brands are approved by FDA for use in SLE)	Prednisone, prednisolone: 0.5–1 mg/kg per day for severe SLE 0.07–0.3 mg/kg per day or qod for milder disease	A2R/ACE antagonists, antiarrhythmics class III, cyclosporine, NSAIDs and salicylates, phenothiazines, phenytoins, quinolones, rifampin, risperidone, thiazides, sulfonylureas, warfarin	Infection, VZV infection, hypertension, hyperglycemia, hypokalemia, acne, allergic reactions, anxiety, aseptic necrosis of bone, cushingoid changes, CHF, fragile skin, insomnia, menstrual irregularities, mood swings, osteoporosis, psychosis
Methylprednisolone sodium succinate, IV[a] (FDA approved for lupus nephritis)	For severe disease, 1 g IV qd × 3 days	As for oral glucocorticoids	As for oral glucocorticoids (if used repeatedly); anaphylaxis
Cyclophosphamide[b] IV	Low dose (for whites of northern European backgrounds): 500 mg every 2 weeks for 6 doses, then begin maintenance with MMF or AZA. High dose: 7–25 mg/kg q month × 6; consider mesna administration with dose	Allopurinol, bone marrow suppressants, colony-stimulating factors, doxorubicin, rituximab, succinylcholine, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, hemorrhagic cystitis (less with IV), carcinoma of the bladder, alopecia, nausea, diarrhea, malaise, malignancy, ovarian and testicular failure. Ovarian failure is probably not a problem with low dose.
Oral	1.5–3 mg/kg per day; decrease dose for CrCl <25 mL/min		

(continued)

TABLE 4-5

MEDICATIONS FOR THE MANAGEMENT OF SLE (CONTINUED)

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
Mycophenolate mofetil (MMF)[b] or mycophenolic acid (MPA)	MMF: 2–3 g/d PO for induction therapy, 1–2 g/d for maintenance therapy; max 1 g bid if CrCl <25 mL/min MPA: 360–1080 mg bid; caution if CrCl <25 mL/min	Acyclovir, antacids, azathioprine, bile acid-binding resins, ganciclovir, iron, salts, probenecid, oral contraceptives	Infection, leukopenia, anemia, thrombocytopenia, lymphoma, lymphoproliferative disorders, malignancy, alopecia, cough, diarrhea, fever, GI symptoms, headache, hypertension, hypercholesterolemia, hypokalemia, insomnia, peripheral edema, elevated liver enzymes, tremor, rash
Azathioprine (AZA)[b]	2–3 mg/kg per day PO for induction; 1–2 mg/kg per day for maintenance; decrease frequency of dose if CrCl <50 mL/min	ACE inhibitors, allopurinol, bone marrow suppressants, interferons, mycophenolate mofetil, rituximab, warfarin, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, pancreatitis, hepatotoxicity, malignancy, alopecia, fever, flulike illness, GI symptoms
Belimumab	10 mg/kg IV wks 0, 2, and 4, then monthly	IVIg	Infusion reactions, allergy, infections probable
Rituximab (for patients resistant to above therapies)	375 mg/m^2 q wk × 4 or 1 g q 2 wks × 2	IVIg	Infection (including PML), infusion reactions, headache, arrhythmias, allergic responses

[a]Indicates medication is approved for use in SLE by the U.S. Food and Drug Administration.
[b]Indicates the medication has been used with glucocorticoids in the trials showing efficacy.
Abbreviations: A2R, angiotensin II receptor; ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; IVIg, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus; SPF, sun protection factor; VZV, varicella-zoster virus.

PULMONARY MANIFESTATIONS

The most common pulmonary manifestation of SLE is pleuritis with or without pleural effusion. This manifestation, when mild, may respond to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs); when more severe, patients require a brief course of glucocorticoid therapy. Pulmonary infiltrates also occur as a manifestation of active SLE and are difficult to distinguish from infection on imaging studies. Life-threatening pulmonary manifestations include interstitial inflammation leading to fibrosis, shrinking lung syndrome, and intraalveolar hemorrhage; all of these probably require early aggressive immunosuppressive therapy as well as supportive care.

CARDIAC MANIFESTATIONS

Pericarditis is the most frequent cardiac manifestation; it usually responds to anti-inflammatory therapy and infrequently leads to tamponade. More serious cardiac manifestations are myocarditis and fibrinous endocarditis of Libman-Sacks. The endocardial involvement can lead to valvular insufficiencies, most commonly of the mitral or aortic valves, or to embolic events. It has not been proven that glucocorticoid or other immunosuppressive therapies lead to improvement of lupus myocarditis or endocarditis, but it is usual practice to administer a trial of high-dose steroids along with appropriate supportive therapy for heart failure, arrhythmia, or embolic events. As discussed above, patients with SLE are at increased risk for myocardial infarction, usually due to accelerated atherosclerosis, which probably results from immune attack, chronic inflammation, and/or chronic oxidative damage to arteries.

HEMATOLOGIC MANIFESTATIONS

The most frequent hematologic manifestation of SLE is anemia, usually normochromic normocytic, reflecting chronic illness. Hemolysis can be rapid in onset and severe, requiring high-dose glucocorticoid therapy, which is effective in most patients. Leukopenia is also common and almost always consists of lymphopenia, not granulocytopenia; lymphopenia rarely predisposes to infections and by itself usually does not require therapy. Thrombocytopenia may be a recurring problem. If platelet counts are >40,000/μL and abnormal bleeding is absent, therapy may not be required. High-dose glucocorticoid therapy (e.g., 1 mg/kg per day of prednisone or equivalent) is usually effective for the first few episodes of severe thrombocytopenia. Recurring or prolonged hemolytic anemia or thrombocytopenia, or disease requiring an unacceptably

high dose of daily glucocorticoids, should be treated with an additional strategy (see "Management of Systemic Lupus Erythematosus" below).

GASTROINTESTINAL MANIFESTATIONS

Nausea, sometimes with vomiting, and diarrhea can be manifestations of an SLE flare, as can diffuse abdominal pain probably caused by autoimmune peritonitis and/or intestinal vasculitis. Increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are common when SLE is active. T ese manifestations usually improve promptly during systemic glucocorticoid therapy. Vasculitis involving the intestine may be life-threatening; perforations, ischemia, bleeding, and sepsis are frequent complications. Aggressive immunosuppressive therapy with high-dose glucocorticoids is recommended for short-term control; evidence of recurrence is an indication for additional therapies.

OCULAR MANIFESTATIONS

Sicca syndrome (Sjögren's syndrome; **Chap. 9**) and nonspecific conjunctivitis are common in SLE and rarely threaten vision. In contrast, retinal vasculitis and optic neuritis are serious manifestations: blindness can develop over days to weeks. Aggressive immunosuppression is recommended, although there are no controlled trials to prove effectiveness. Complications of systemic and intraorbital glucocorticoid therapy include cataracts (common) and glaucoma.

LABORATORY TESTS

Laboratory tests serve (1) to establish or rule out the diagnosis; (2) to follow the course of disease, particularly to suggest that a flare is occurring or organ damage is developing; and (3) to identify adverse effects of therapies.

TESTS FOR AUTOANTIBODIES

Diagnostically, the most important autoantibodies to detect are ANA because the test is positive in >95% of patients, usually at the onset of symptoms (Tables 4-1 and 4-3). A few patients develop ANA within 1 year of symptom onset; repeated testing may thus be useful. ANA tests using immunofluorescent methods are more reliable than enzyme-linked immunosorbent assays (ELISAs) and/or bead assays, which have less specificity. ANA-negative lupus exists but is rare in adults and is usually associated with other autoantibodies (anti-Ro or anti-DNA). High-titer IgG antibodies to double-stranded DNA (dsDNA) (but not to single-stranded DNA) are specific for SLE. ELISA and immunofluorescent reactions of sera with the dsDNA in the flagellate Crithidia luciliae have ~60% sensitivity for SLE; identification of high-avidity anti-dsDNA in the Farr assay is not as sensitive but may correlate better with risk for nephritis. Titers of anti-dsDNA vary over time. In some patients, increases in quantities of anti-dsDNA herald a flare, particularly of nephritis or vasculitis, especially when associated with declining levels of C3 or C4 complement. Antibodies to Sm are also specific for SLE and assist in diagnosis; anti-Sm antibodies do not usually correlate with disease activity or clinical manifestations. Antiphospholipid antibodies are not specific for SLE, but their presence fulfills one classification criterion, and they identify patients at increased risk for venous or arterial clotting, thrombocytopenia, and fetal loss. T ere are three widely accepted tests that measure different antibodies (anticardiolipin, anti-β_2-glycoprotein, and the lupus anticoagulant). ELISA is used for anticardiolipin and anti-β_2-glycoprotein (both internationally standardized with good reproducibility); a sensitive phospholipid-based activated prothrombin time such as the dilute Russell venom viper test is used to identify the lupus anticoagulant. T e higher the titers of IgG anticardiolipin (>40 IU is considered high), and the greater the number of different antiphospholipid antibodies that are detected, the greater is the risk for a clinical episode of clotting. Quantities of antiphospholipid antibodies may vary markedly over time; repeated testing is justified if clinical manifestations of the antiphospholipid syndrome (APS) appear **(Chap. 5)**. To classify a patient as having APS, with or without SLE, by international criteria requires the presence of one or more clotting episodes and/or repeated fetal losses plus at least two positive tests for antiphospholipid antibodies, at least 12 weeks apart; however, many patients with APS do not meet these stringent criteria, which are intended for inclusion of patients into studies.

An additional autoantibody test with predictive value (not used for diagnosis) detects anti-Ro/SS-A, which indicates increased risk for neonatal lupus, sicca syndrome, and SCLE. Women with child-bearing potential and SLE should be screened for antiphospholipid antibodies and anti-Ro, because both antibodies have the potential to cause fetal harm.

STANDARD TESTS FOR DIAGNOSIS

Screening tests for complete blood count, platelet count, and urinalysis may detect abnormalities that contribute to the diagnosis and influence management decisions.

TESTS FOR FOLLOWING DISEASE COURSE

It is useful to follow tests that indicate the status of organ involvement known to be present during SLE flares.

T ese might include urinalysis for hematuria and proteinuria, hemoglobin levels, platelet counts, and serum levels of creatinine or albumin. T ere is great interest in identification of additional markers of disease activity. Candidates include levels of anti-DNA and anti-C1q antibodies, several components of complement (C3 is most widely available), activated complement products (including those that bind to the C4d receptor on erythrocytes), IFN-inducible gene expression in peripheral blood cells, serum levels of BLyS (B lymphocyte stimulator, also called BAFF), and urinary levels of TNF-like weak inducer of apoptosis (TWEAK), neutrophil gelatinase-associated lipocalin (NGAL), or monocyte chemotactic protein 1 (MCP-1). None is uniformly agreed upon as a reliable indicator of flare or of response to therapeutic interventions. It is likely that a panel of multiple proteins will be developed to predict both impending flare and response to recently instituted therapies. For now, the physician should determine for each patient whether certain laboratory test changes predict flare. If so, altering therapy in response to these changes may be advisable (30 mg of prednisone daily for 2 weeks has been shown to prevent flares in patients with rising anti-DNA plus falling complement). In addition, given the increased prevalence of atherosclerosis in SLE, it is advisable to follow the recommendations of the National Cholesterol Education Program for testing and treatment, including scoring of SLE as an independent risk factor, similar to diabetes mellitus.

MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

T ere is no cure for SLE, and complete sustained remissions are rare. T erefore, the physician should plan to induce remissions of acute flares and then maintain improvements with strategies that suppress symptoms to an acceptable level and prevent organ damage. Usually patients will endure some adverse effects of medications. T erapeutic choices depend on (1) whether disease manifestations are life-threatening or likely to cause organ damage, justifying aggressive therapies; (2) whether manifestations are potentially reversible; and (3) the best approaches to preventing complications of disease and its treatments. T erapies, doses, and adverse effects are listed in Table 4-5.

CONSERVATIVE THERAPIES FOR MANAGEMENT OF NON-LIFE-THREATENING DISEASE

Among patients with fatigue, pain, and autoantibodies indicative of SLE, but without major organ involvement, management can be directed to suppression of symptoms. Analgesics and antimalarials are mainstays. NSAIDs are useful analgesics/anti-inflammatories, particularly for arthritis/arthralgias. However, two major issues indicate caution in using NSAIDs. First, SLE patients compared with the general population are at increased risk for NSAID-induced aseptic meningitis, elevated serum transaminases, hypertension, and renal dysfunction. Second, all NSAIDs, particularly those that inhibit cyclooxygenase-2 specifically, may increase risk for myocardial infarction. Acetaminophen to control pain may be a good strategy, but NSAIDs are more effective in some patients. T e relative hazards of NSAIDs compared with low-dose glucocorticoid therapy have not been established. Antimalarials (hydroxychloroquine, chloroquine, and quinacrine) often reduce dermatitis, arthritis, and fatigue. A randomized, placebo-controlled, prospective trial has shown that withdrawal of hydroxychloroquine results in increased numbers of disease flares; hydroxychloroquine also reduces accrual of tissue damage, including renal damage, over time. Because of potential retinal toxicity, patients receiving antimalarials should undergo ophthalmologic examinations annually. A placebo-controlled prospective trial suggests that administration of dehydroepiandrosterone may reduce disease activity. If quality of life is inadequate despite these conservative measures, treatment with low doses of systemic glucocorticoids may be necessary. T e clinician may also consider treatment with belimumab (anti-BLyS) in these patients, although published clinical trials enrolled patients who had failed to respond to conservative therapies. Lupus dermatitis should be managed with topical sunscreens, antimalarials, topical glucocorticoids, and/or tacrolimus, and if severe or unresponsive, systemic glucocorticoids with or without mycophenolate mofetil.

LIFE-THREATENING SLE: PROLIFERATIVE FORMS OF LUPUS NEPHRITIS

Guidelines for management of lupus nephritis have been published recently by the American College of Rheumatology and the European League Against Rheumatism (encompassed and referenced in Fig. 4-2 and Table 4-5). T e mainstay of treatment for any inflammatory life-threatening or organ-threatening manifestations of SLE is systemic glucocorticoids (0.5–1 mg/kg per day PO or 500–1000 mg of methylprednisolone sodium succinate IV daily for 3 days followed by 0.5–1 mg/kg of daily prednisone or equivalent). Evidence that glucocorticoid therapy is life-saving comes from retrospective studies from the predialysis era; survival was significantly better in people with DPGN treated with high-dose daily glucocorticoids (40–60 mg of prednisone daily for 4–6 months) versus lower doses. Currently, high doses are recommended for much shorter periods; recent trials of interventions for severe SLE use 4–6 weeks of 0.5–1 mg/kg

per day of prednisone or equivalent. T ereafter, doses are tapered as rapidly as the clinical situation permits, usually to a maintenance dose ranging from 5 to 10 mg of prednisone or equivalent per day. Most patients with an episode of severe SLE require many years of maintenance therapy with low-dose glucocorticoids, which can be increased to prevent or treat disease flares. Frequent attempts to gradually reduce the glucocorticoid requirement are recommended because virtually everyone develops important adverse effects (Table 4-5). High-quality clinical studies regarding initiating therapy for severe, active SLE with IV pulses of high-dose glucocorticoids are not available. Most recent clinical trials in lupus nephritis have initiated therapy with high-dose IV glucocorticoid pulses (500–1000 mg daily for 3–5 days). T is approach must be tempered by safety considerations, such as the presence of conditions adversely affected by glucocorticoids (e.g., infection, hyperglycemia, hypertension, osteoporosis).

Cytotoxic/immunosuppressive agents added to glucocorticoids are recommended to treat serious SLE. Almost all prospective controlled trials in SLE involving cytotoxic agents have been conducted in combination with glucocorticoids in patients with lupus nephritis. T erefore, the following recommendations apply to treatment of nephritis. Either cyclophosphamide (an alkylating agent) or mycophenolate mofetil (a relatively lymphocyte-specific inhibitor of inosine monophosphatase and therefore of purine synthesis) is an acceptable choice for induction of improvement in severely ill patients; azathioprine (a purine analogue and cycle-specific antimetabolite) may be effective but is slower to influence response and associated with more flares. In patients whose renal biopsies show ISN grade III or IV disease, early treatment with combinations of glucocorticoids and cyclophosphamide reduces progression to ESRD and death. Shorter-term studies with glucocorticoids plus mycophenolate mofetil (prospective randomized trials of 6 months, follow-up studies of 36 months) show that this regimen is similar to cyclophosphamide in achieving improvement. Comparisons are complicated by effects of race, since higher proportions of African Americans (and other non-Asian, nonwhite races) respond to mycophenolate than to cyclophosphamide, whereas similar proportions of whites and Asians respond to each drug. Regarding toxicity, diarrhea is more common with mycophenolate mofetil; amenorrhea, leukopenia, and nausea are more common with cyclophosphamide. Importantly, rates of severe infections and death are similar in meta-analyses. Two different regimens of IV cyclophosphamide are available. For white patients with northern European backgrounds, low doses of cyclophosphamide (500 mg every 2 weeks for six total doses, followed by azathioprine or mycophenolate maintenance) are as effective as standard high doses, with less toxicity. Ten-year follow-up has shown no differences between the high-dose and low-dose groups (death or ESRD in 9–20% of patients in each group). T e majority of the European patients were white; it is not clear whether the data apply to U.S. populations. High-dose cyclophosphamide (500–1000 mg/m^2 body surface area given monthly IV for 6 months, followed by azathioprine or mycophenolate maintenance) is an acceptable approach for patients with severe nephritis (e.g., multiple cellular crescents and/or fibrinoid necrosis on renal biopsy, or rapidly progressive glomerulonephritis). Cyclophosphamide and mycophenolate responses begin 3–16 weeks after treatment is initiated, whereas glucocorticoid responses may begin within 24 h.

For maintenance therapy, mycophenolate and azathioprine probably are similar in ef cacy and toxicity; both are safer than cyclophosphamide. In a recently published multicenter study, mycophenolate was superior to azathioprine in maintaining renal function and survival in patients who responded to induction therapy with either cyclophosphamide or mycophenolate. T e incidence of ovarian failure, a common effect of high-dose cyclophosphamide therapy (but probably not of low-dose therapy), can be reduced by treatment with a gonadotropin-releasing hormone agonist (e.g., leuprolide 3.75 mg intramuscularly) prior to each monthly cyclophosphamide dose. Patients with high serum creatinine levels (e.g., ≥265 μmol/L [≥3.0 mg/dL]) many months in duration and high chronicity scores on renal biopsy are not likely to respond to any of these therapies. In general, it may be better to induce improvement in an African-American or Hispanic patient with proliferative glomerulonephritis with mycophenolate mofetil (2–3 g daily) rather than cyclophosphamide, with the option to switch if no evidence of response is detectable after 3–6 months of treatment. For whites and Asians, induction with either mycophenolate mofetil or cyclophosphamide is acceptable. Cyclophosphamide may be discontinued when it is clear that a patient is improving. T e number of SLE flares is reduced by maintenance therapy with mycophenolate mofetil (1.5–2 g daily) or azathioprine (1–2.5 mg/kg per day). Both cyclophosphamide and mycophenolate mofetil are potentially teratogenic; patients should be off either medication for at least 3 months before attempting to conceive. Azathioprine can be used if necessary to control active SLE in patients who are pregnant. If azathioprine is used either for induction or maintenance therapy, patients may be prescreened for homozygous deficiency of the TMPT enzyme (which is required to metabolize the 6-mercaptopurine product of azathioprine) because they are at higher risk for bone marrow suppression.

Good improvement occurs in ~80% of lupus nephritis patients receiving either cyclophosphamide or mycophenolate at 1–2 years of follow-up. However,

in some studies, at least 50% of these individuals have flares of nephritis over the next 5 years, and re-treatment is required; such individuals are more likely to progress to ESRD. Long-term outcome of lupus nephritis to most interventions is better in whites than in African Americans. Methotrexate (a folinic acid antagonist) may have a role in the treatment of arthritis and dermatitis but probably not in nephritis or other life-threatening disease. Small controlled trials (in Asia) of leflunomide, a relatively lymphocyte-specific pyrimidine antagonist licensed for use in rheumatoid arthritis, have suggested it can suppress disease activity in some SLE patients. Cyclosporine and tacrolimus, which inhibit production of IL-2 and T lymphocyte functions, have not been studied in prospective controlled trials in SLE in the United States; several studies in Asia have shown they are effective in lupus nephritis. Because they have potential nephrotoxicity but little bone marrow toxicity, the author uses them for periods of a few months in patients with steroid-resistant cytopenias of SLE or in steroid-resistant patients who have developed bone marrow suppression from standard cytotoxic agents.

Use of biologics directed against B cells for active SLE is under intense study. Use of anti-CD20 (rituximab), particularly in patients with SLE who are resistant to the more standard combination therapies discussed above, is controversial. Several open trials have shown ef cacy in a majority of such patients, both for nephritis and for extrarenal lupus. However, recent prospective placebo-controlled randomized trials, one in renal and one in nonrenal SLE, did not show a difference between anti-CD20 and placebo when added to standard combination therapies. In contrast, recent trials of standard therapy plus belimumab (anti-BLyS, which binds soluble BLyS/BAFF, which is required for maturation of naïve and transitional B cells to plasma cells and memory B cells) showed improvement in 51% of SLE patients compared to 36% of those on placebo; these differences were statistically significant. T e U.S. Food and Drug Administration (FDA) has approved belimumab for treatment of seropositive patients with SLE who have failed standard treatments. T e belimumab trial did not include patients with active nephritis or CNS disease. Post hoc analyses have shown that the SLE patient most likely to respond to belimumab has fairly robust clinical activity (a Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score of ≥10), positive anti-DNA, and low serum complement. SLEDAI is a widely used measure of SLE disease activity; scores >3 reflect clinically active disease. At this time, it is useful to add belimumab to the therapeutic armamentarium in SLE, and it is clear that some patients benefit. However, its role in management of lupus nephritis is not yet known.

SPECIAL CONDITIONS IN SLE THAT MAY REQUIRE ADDITIONAL OR DIFFERENT THERAPIES

Crescentic lupus nephritis

T e presence of cellular or fibrotic crescents in glomeruli with proliferative glomerulonephritis indicates a worse prognosis than in patients without this feature. T ere are no large prospective multinational controlled trials showing ef cacy of cyclophosphamide, mycophenolate, cyclosporine, or tacrolimus in such cases. Most authorities currently recommend that high-dose cyclophosphamide is the induction therapy of choice, in addition to high-dose glucocorticoids. One prospective trial from China showed superiority of mycophenolate to cyclophosphamide.

Membranous lupus nephritis

Most SLE patients with membranous (INS-V) nephritis also have proliferative changes and should be treated for proliferative disease. However, some have pure membranous changes. Treatment for this group is less well defined. Some authorities do not recommend immunosuppression unless proteinuria is in the nephrotic range (although treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is recommended). In those patients, recent prospective controlled trials suggest that alternate-day glucocorticoids plus cyclophosphamide or mycophenolate mofetil or cyclosporine are all effective in the majority of patients in reducing proteinuria. It is more controversial whether they preserve renal function over the long term.

Pregnancy and lupus

Fertility rates for men and women with SLE are probably normal. However, rate of fetal loss is increased (approximately two- to threefold) in women with SLE. Fetal demise is higher in mothers with high disease activity, antiphospholipid antibodies, and/or active nephritis. Suppression of disease activity can be achieved by administration of systemic glucocorticoids. A placental enzyme, 11-β-dehydrogenase 2, deactivates glucocorticoids; it is more effective in deactivating prednisone and prednisolone than the fluorinated glucocorticoids dexamethasone and betamethasone. Glucocorticoids are listed by the FDA as pregnancy category A (no evidence of teratogenicity in human studies); cyclosporine, tacrolimus, and rituximab are listed as category C (may be teratogenic in animals but no good evidence in humans); azathioprine, hydroxychloroquine, mycophenolate mofetil, and cyclophosphamide are category D (there is evidence of teratogenicity in humans, but benefits might outweigh risks in certain situations); and methotrexate is category

X (risks outweigh benefits). T erefore, active SLE in pregnant women should be controlled with hydroxychloroquine and, if necessary, prednisone/prednisolone at the lowest effective doses for the shortest time required. Azathioprine may be added if these treatments do not suppress disease activity. Adverse effects of prenatal glucocorticoid exposure (primarily betamethasone) on offspring may include low birth weight, developmental abnormalities in the CNS, and predilection toward adult metabolic syndrome. It is likely that each of these glucocorticoids and immunosuppressive medications gets into breast milk, at least in low levels; patients should consider not breastfeeding if they need therapy for SLE. In SLE patients with antiphospholipid antibodies (on at least two occasions) and prior fetal losses, treatment with heparin (usually low-molecular-weight) plus low-dose aspirin has been shown in prospective controlled trials to increase significantly the proportion of live births; however, a recent prospective trial showed no differences in fetal outcomes in women taking aspirin compared to those taking aspirin plus low-molecular-weight heparin. An additional potential problem for the fetus is the presence of antibodies to Ro, sometimes associated with neonatal lupus consisting of rash and congenital heart block with or without cardiomyopathy. T e cardiac manifestations can be life-threatening; therefore the presence of anti-Ro requires vigilant monitoring of fetal heart rates with prompt intervention (delivery if possible) if distress occurs. Recent evidence shows that hydroxychloroquine treatment of an anti-Ro-positive mother whose infant develops congenital heart block significantly reduces the chance that subsequent fetuses will develop heart block. T ere is some evidence that dexamethasone treatment of a mother in whom first- or second-degree heart block is detected in utero may sometimes prevent progression of heart block. Women with SLE usually tolerate pregnancy without disease flares. However, a small proportion develops severe flares requiring aggressive glucocorticoid therapy or early delivery. Poor maternal outcomes are highest in women with active nephritis or irreversible organ damage in kidneys, brain, or heart.

Lupus and antiphospholipid syndrome (APS)

Patients with SLE who have venous or arterial clotting and/or repeated fetal losses and at least two positive tests for antiphospholipid antibodies have APS and should be managed with long-term anticoagulation **(Chap. 5)**. A target international normalized ratio (INR) of 2.0–2.5 is recommended for patients with one episode of venous clotting; an INR of 3.0–3.5 is recommended for patients with recurring clots or arterial clotting, particularly in the CNS. Recommendations are based on both retrospective and prospective studies of posttreatment clotting events and adverse effects from anticoagulation.

Microvascular thrombotic crisis (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome)

T is syndrome of hemolysis, thrombocytopenia, and microvascular thrombosis in kidneys, brain, and other tissues carries a high mortality rate and occurs most commonly in young individuals with lupus nephritis. T e most useful laboratory tests are identification of schistocytes on peripheral blood smears, elevated serum levels of lactate dehydrogenase, and antibodies to ADAMS13. Plasma exchange or extensive plasmapheresis is usually life-saving; most authorities recommend concomitant glucocorticoid therapy; there is no evidence that cytotoxic drugs are effective.

Lupus dermatitis

Patients with any form of lupus dermatitis should minimize exposure to ultraviolet light, using appropriate clothing and sunscreens with a sun protection factor of at least 30. Topical glucocorticoids and antimalarials (such as hydroxychloroquine) are effective in reducing lesion severity in most patients and are relatively safe. Systemic treatment with retinoic acid is a useful strategy in patients with inadequate improvement on topical glucocorticoids and antimalarials; adverse effects are potentially severe (particularly fetal abnormalities), and there are stringent reporting requirements for its use in the United States. Extensive, pruritic, bullous, or ulcerating dermatitides usually improve promptly after institution of systemic glucocorticoids; tapering may be accompanied by flare of lesions, thus necessitating use of a second medication such as hydroxychloroquine, retinoids, or cytotoxic medications such as methotrexate, azathioprine, or mycophenolate mofetil. In therapy-resistant lupus dermatitis there are reports of success with topical tacrolimus (caution must be exerted because of the possible increased risk for malignancies) or with systemic dapsone or thalidomide (the extreme danger of fetal deformities from thalidomide requires permission from and supervision by the supplier).

PREVENTIVE THERAPIES

Prevention of complications of SLE and its therapy include providing appropriate vaccinations (the administration of influenza and pneumococcal vaccines has been studied in patients with SLE; flare rates are similar to those receiving placebo) and suppressing recurrent urinary tract infections. Vaccination with attenuated live viruses is generally discouraged in patients who are immunosuppressed. Strategies to prevent osteoporosis should be initiated in most patients likely to require long-term glucocorticoid therapy and/or with other predisposing factors. Postmenopausal women can be protected from steroid-induced osteoporosis with either bisphosphonates or denosumab. Safety

of long-term use of these strategies in premenopausal women is not well established. Control of hypertension and appropriate prevention strategies for atherosclerosis, including monitoring and treatment of dyslipidemias, management of hyperglycemia, and management of obesity, are recommended.

EXPERIMENTAL THERAPIES

Studies of highly targeted experimental therapies for SLE are in progress. T ey include targeting (1) activated B lymphocytes with anti-CD22 or TACI-Ig, (2) inhibition of IFN-α, (3) inhibition of B/T cell second signal coactivation with CTLA-Ig, (4) inhibition of innate immune activation via TLR7 or TLR7 and 9, (5) induction of regulatory T cells with peptides from immunoglobulins or autoantigens; (6) suppression of T cells, B cells, and monocyte/macrophages with laquinimod; and (7) inhibition of lymphocyte activation by blockade of Jak/Stat. A few studies have used vigorous untargeted immunosuppression with high-dose cyclophosphamide plus anti-T cell strategies, with rescue by transplantation of autologous hematopoietic stem cells for the treatment of severe and refractory SLE. One U.S. report showed an estimated mortality rate over 5 years of 15% and sustained remission in 50%. It is hoped that in the next edition of this text, we will be able to recommend more effective and less toxic approaches to treatment of SLE based on some of these strategies.

PATIENT OUTCOMES, PROGNOSIS, AND SURVIVAL



Survival in patients with SLE in the United States, Canada, Europe, and China is approximately 95% at 5 years, 90% at 10 years, and 78% at 20 years. In the United States, African Americans and Hispanic Americans with a mestizo heritage have a worse prognosis than whites, whereas Africans in Africa and Hispanic Americans with a Puerto Rican origin do not. T e relative importance of gene mixtures and environmental differences accounting for ethnic differences is not known. Poor prognosis (~50% mortality in 10 years) in most series is associated with (at the time of diagnosis) high serum creatinine levels (>124 μmol/L [>1.4 mg/dL]), hypertension, nephrotic syndrome (24-h urine protein excretion >2.6 g), anemia (hemoglobin <124 g/L [<12.4 g/dL]), hypoalbuminemia, hypocomplementemia, antiphospholipid antibodies, male sex, ethnicity (African American, Hispanic with mestizo heritage), and low socioeconomic status. Data regarding outcomes in SLE patients with renal transplants show mixed results: some series show a twofold increase in graft rejection compared to patients with other causes of ESRD, whereas others show no differences. Overall patient survival is comparable (85% at 2 years). Lupus nephritis occurs in approximately 10% of transplanted kidneys. Disability in patients with SLE is common due primarily to chronic fatigue, arthritis, and pain, as well as renal disease. As many as 25% of patients may experience remissions, sometimes for a few years, but these are rarely permanent. T e leading causes of death in the first decade of disease are systemic disease activity, renal failure, and infections; subsequently, thromboembolic events become increasingly frequent causes of mortality.

DRUG-INDUCED LUPUS

T is is a syndrome of positive ANA associated with symptoms such as fever, malaise, arthritis or intense arthralgias/myalgias, serositis, and/or rash. T e syndrome appears during therapy with certain medications and biologic agents, is predominant in whites, has less female predilection than SLE, rarely involves kidneys or brain, is rarely associated with anti-dsDNA, is commonly associated with antibodies to histones, and usually resolves over several weeks after discontinuation of the offending medication. T e list of substances that can induce lupus-like disease is long. Among the most frequent are the antiarrhythmics procainamide, disopyramide, and propafenone; the antihypertensive hydralazine; several angiotensin-converting enzyme inhibitors and beta blockers; the antithyroid propylthiouracil; the antipsychotics chlorpromazine and lithium; the anticonvulsants carbamazepine and phenytoin; the antibiotics isoniazid, minocycline, and nitrofurantoin (Macrodantin); the antirheumatic sulfasalazine; the diuretic hydrochlorothiazide; the antihyperlipidemics lovastatin and simvastatin; and IFNs and TNF inhibitors. ANA usually appears before symptoms; however, many of the medications mentioned above induce ANA in patients who never develop symptoms of drug-induced lupus. It is appropriate to test for ANA at the first hint of relevant symptoms and to use test results to help decide whether to withdraw the suspect agent.

CHAPTER 5

ANTIPHOSPHOLIPID SYNDROME

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DEFINITIONS

Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity. The major autoantibodies detected in the patient's sera are directed against phospholipid (PL)-binding plasma proteins, mainly against a 43-kDa plasma apolipoprotein known as β2 glycoprotein I (β2GPI) and prothrombin. The plasma concentration of β2GPI is 50–200 μg/mL. β2GPI consists of 326 amino acids arranged in five domains (I through V). Domain V forms a positively charged patch, suitable to interact with negatively charged PL. In plasma, β2GPI has a circular conformation with domain V binding to and concealing the B cell epitopes lying on domain I. Another group of antibodies termed lupus anticoagulant (LA) elongate clotting times in vitro; this elongation is not corrected by adding normal plasma to the detection system **(Table 5-1)**. Patients with APS often possess antibodies recognizing Treponema pallidum PL/cholesterol complexes, which are detected as biologic false-positive serologic tests for syphilis (BFP-STS) and Venereal Disease Research Laboratory (VDRL) tests. APS may occur alone (primary) or in association with any other autoimmune disease (secondary). Catastrophic APS (CAPS) is defined as a rapidly progressive thromboembolic disease involving simultaneously three or more organs, organ systems, or tissues leading to corresponding functional defects.

EPIDEMIOLOGY

Anti-PL (aPL)-binding plasma protein antibodies occur in 1–5% of the general population. Their prevalence increases with age; however, it is questionable whether they induce thrombotic events in elderly individuals. One-third of patients with systemic lupus erythematosus (SLE) **(Chap. 4)** possess these antibodies, whereas their prevalence in other autoimmune connective tissue disorders, such as systemic sclerosis (scleroderma), Sjögren's syndrome, dermatomyositis, rheumatoid arthritis, and early undifferentiated connective tissue disease, ranges from 6 to 15%. One-third of aPL-positive individuals experience thrombotic events or pregnancy morbidity.

PATHOGENESIS

The trigger for the induction of antibodies to PL-binding proteins is not known. However infections, oxidative stress, major physical stresses such as surgery, and discontinuation of anticoagulant treatment may induce the exacerbation of the disease. Experimental data have shown that these phenomena are induced via (1) conformational changes of β2GPI either complexed with microbial antigens or dimerization through interaction with endothelial cell surface receptor annexin 2/TLR4, the platelet receptors apolipoprotein E receptor 2′ (apoER2′) and/or GPIb/IX/V receptor, and/or the chemokine platelet factor 4 (PF4); or (2) impaired defensive mechanisms such as reduced generation of endothelial nitric oxide synthase. Adherence of β2GPI to apoER2′, GPIb/IX/V receptor, and/or PF4 induces activation of endothelial cells, platelets, and monocytes. This process activates downstream pathways such as p38 mitogen-activated protein (p38 MAP) kinase and nuclear factor (NF)-κB, leading to the following events: secretion of proinflammatory cytokines, such as interleukin (IL) 1, IL-6, and IL-8; the expression of adhesion molecules; inhibition of cell-surface plasminogen activation; and expression of tissue factor. The above events change the phenotype of these cells to a prothrombotic form. In addition, anti-β2GPI antibodies induce fetal injury in mice through complement activation,

TABLE 5-1

CLASSIFICATION AND NOMENCLATURE OF ANTIPHOSPHOLIPID ANTIBODIES

NAME	ASSAY FOR THEIR DETECTION	COMMENTS
Antibodies against cardiolipin (aCL)	Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid	aCL from patients with APS recognize β2GPI existing in the human serum as well as in bovine serum, which is used to block the non-specific bindings sites on the ELISA plate. CL simply stabilizes β2GPI at high concentration on the polystyrene surface.
Antibodies against β2GPI (anti-β2GPI)	ELISA using as antigen af nity purified or recombinant β2GPI in the absence of PL	Antibodies recognize β2GPI bound in the absence of CL to an oxidized polystyrene surface, where oxygen atoms in the moieties C-O or C=O were introduced by γ-irradiation.
Lupus anticoagulant (LA)	Activated partial thromboplastin time (aPTT) Kaolin clotting time (KCT) Dilute Russel viper venom test (DRVVT)	Antibodies recognize β2GPI or prothrombin (PT) and elongate aPTT, implying that they interfere with the generation of thrombin by prothrombin. Prolongation of the clotting times is an in vitro phenomenon, and LA induces thromboses in vivo.

Abbreviations: APL, antiphospholipid syndrome; β2GPI, β2 glycoprotein I; PL, phospholipid.

as shown by the evidence that C4-deficient mice were protected from fetal injury.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Clinical manifestations represent mainly a direct or indirect expression of venous or arterial thrombosis and/or pregnancy morbidity **(Table 5-2)**. Clinical features associated with venous thrombosis are superficial and deep vein thrombosis, cerebral venous thrombosis, signs and symptoms of intracranial hypertension, retinal vein thrombosis, pulmonary emboli, pulmonary arterial hypertension, and Budd-Chiari syndrome.

TABLE 5-2

CLINICAL FEATURES OF ANTIPHOSPHOLIPID SYNDROME

MANIFESTATION	%
Venous Thrombosis and Related Consequences	
Deep vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-Sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone	6
Multi-infarct dementia	3
Neurologic Manifestations of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5
Renal Manifestations Due to Various Reasons (Renal Artery/Renal Vein/Glomerular Thrombosis, Fibrous Intima Hyperplasia)	3
Osteoarticular Manifestations	
Arthralgia	39
Arthritis	27
Obstetric Manifestations (Referred to the Number of Pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the Number of Pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss (≥10 weeks)	17
Premature birth among the live births	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Source: Adapted from R Cervera et al: Arthritis Rheum 46:1019, 2002.

Livedo reticularis consists of a mottled reticular vascular pattern that appears as a lace-like, purplish discoloration of the skin. It is probably caused by swelling of the venules owing to obstruction of capillaries by

thrombi. T is clinical manifestation correlates with vascular lesions such as those in the central nervous system as well as aseptic bone necrosis. Arterial thrombosis is manifested as migraines, cognitive dysfunction, transient ischemic attacks, stroke, myocardial infarction, arterial thrombosis of upper and lower extremities, ischemic leg ulcers, digital gangrene, avascular necrosis of bone, retinal artery occlusion leading to painless transient vision loss, renal artery stenosis, and glomerular lesions, as well as infarcts of spleen, pancreas, and adrenals. Libman-Sacks endocarditis consists of very small vegetations, histologically characterized by organized platelet-fibrin microthrombi surrounded by growing fibroblasts and macrophages. Glomerular lesions are manifested with hypertension, mildly elevated serum creatinine levels, proteinuria, and mild hematuria. Histologically, these lesions are characterized in an acute phase by thrombotic microangiopathy involving glomerular capillaries, and in a chronic phase with fibrous intima hyperplasia, fibrous and/or fibrocellular occlusions of arterioles, and focal cortical atrophy (Table 5-2). Premature atherosclerosis has been recognized as a rare feature of APS. Coombs-positive hemolytic anemia and thrombocytopenia are laboratory findings associated with APS. Discontinuation of therapy, major surgery, infection, and trauma may trigger CAPS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

T e diagnosis of APS should be seriously considered in cases of thrombosis, cerebral vascular accidents in individuals younger than 55 years of age, or pregnancy morbidity in the presence of livedo reticularis or thrombocytopenia. In these cases, aPL antibodies should be measured. T e presence of at least one clinical and one laboratory criterion ensures the diagnosis even in the presence of other causes of thrombophilia. Clinical criteria include: (1) vascular thrombosis defined as one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ; and (2) pregnancy morbidity, defined as (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation; (b) one or more premature births of a morphologically normal neonate before the thirty-fourth week of gestation because of eclampsia, severe preeclampsia, or placental insuf ciency; or (c) three or more unexplained consecutive spontaneous abortions before the tenth week of gestation. Laboratory criteria include (1) LA, (2) anticardiolipin (aCL), and/or (3) anti-β2GPI antibodies, at intermediate or high titers on two occasions, 12 weeks apart.

Differential diagnosis is based on the exclusion of other inherited or acquired causes of thrombophilia, Coombs-positive hemolytic anemia, and thrombocytopenia. Livedo reticularis with or without a painful ulceration on the lower extremities also may be a manifestation of disorders affecting (1) the vascular wall, such as polyarteritis nodosa, SLE, cryoglobulinemia, and lymphomas; or (2) the vascular lumen, such as myeloproliferative disorders, atherosclerosis, hypercholesterolemia, or other causes of thrombophilia.

TREATMENT Antiphospholipid Syndrome

After the first thrombotic event, APS patients should be placed on warfarin for life, aiming to achieve an international normalized ratio (INR) ranging from 2.5 to 3.5, alone or in combination with 80 mg of aspirin daily. Pregnancy morbidity is prevented by a combination of heparin with aspirin 80 mg daily. IV immunoglobulin (IVIg) 400 mg/kg every day for 5 days may also prevent abortions, whereas glucocorticoids are ineffective. Patients with aPL in the absence of any clinical event who are simultaneously positive for aCL, anti-β2GPI, and LA or have SLE are at risk to develop thrombotic events and can be protected by aspirin 80 mg daily.

Some patients with APS and patients with CAPS have recurrent thrombotic events despite appropriate anticoagulation. In these cases, IVIg 400 mg/kg every day for 5 days may be of benefit. Patients with CAPS, who are treated in the intensive care unit, are unable to receive warfarin; in this situation, therapeutic doses of low-molecular-weight heparin should be administered. In cases of heparin-induced thrombocytopenia and thrombosis syndrome, inhibitors of phospholipid-bound activated factor X (FXa), such as fondaparinux 7.5 mg SC daily or rivaroxaban 10 mg PO daily, are effective. T e above drugs are administered by fixed doses and do not require close monitoring; their safety during the first trimester of pregnancy has not been clearly established.

CHAPTER 6

RHEUMATOID ARTHRITIS

Ankoor Shah ■ E. William St. Clair

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. Because it is a systemic disease, RA may result in a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities.

Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. Serum antibodies to cyclic citrullinated peptides (anti-CCPs) are routinely used along with rheumatoid factor as a biomarker of diagnostic and prognostic significance. Advances in imaging modalities have improved our ability to detect joint inflammation and destruction in RA. T e science of RA has taken a major leap forward with the identification of new disease-related genes and further deciphering of the molecular pathways of disease pathogenesis. T e relative importance of these different mechanisms has been highlighted by the observed benefits of the new class of highly targeted biologic and small-molecule therapies. Despite these gains, incomplete understanding of the initiating pathogenic pathways of RA remains a sizable barrier to its cure and prevention.

T e last two decades have witnessed a remarkable improvement in the outcomes of RA. T e historic descriptions of crippling arthritis are currently encountered much less frequently. Much of this progress can be traced to the expanded therapeutic armamentarium and the adoption of early treatment intervention. T e shift in treatment strategy dictates a new mind-set for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for prompt diagnosis and initiation of therapy. Only then will patients achieve their best outcomes.

CLINICAL FEATURES

T e incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. T e presenting symptoms of RA typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting more than 1 h that eases with physical activity. T e earliest involved joints are typically the small joints of the hands and feet. T e initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis. T ose with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or anti-CCP antibodies, and have higher scores for physical disability.

Once the disease process of RA is established, the wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints stand out as the most frequently involved joints **(Fig. 6-1)**. Distal interphalangeal (DIP) joint involvement may occur in RA, but it usually is a manifestation of coexistent osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and "trigger" fingers. Progressive destruction of the joints and soft tissues may lead to chronic, irreversible deformities. Ulnar deviation results from subluxation of the MCP joints, with subluxation of the



FIGURE 6-1
Metacarpophalangeal and proximal interphalangeal joint swelling in rheumatoid arthritis. (Courtesy of the American College of Rheumatology Image Bank.)

proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint ("swan-neck deformity"), flexion of the PIP joint with hyperextension of the DIP joint ("boutonnière deformity"), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint ("Z-line deformity") also may result from damage to the tendons, joint capsule, and other soft tissues in these small joints. Inflammation about the ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna, resulting in a "piano-key movement" of the ulnar styloid. Although metatarsophalangeal (MTP) joint involvement in the feet is an early feature of disease, chronic inflammation of the ankle and midtarsal regions usually comes later and may lead to pes planovalgus ("flat feet"). Large joints, including the knees and shoulders, are often affected in established disease, although these joints may remain asymptomatic for many years after onset.

Atlantoaxial involvement of the cervical spine is clinically noteworthy because of its potential to cause compressive myelopathy and neurologic dysfunction. Neurologic manifestations are rarely a presenting sign or symptom of atlantoaxial disease, but they may evolve over time with progressive instability of C1 on C2. The prevalence of atlantoaxial subluxation has been declining in recent years, and occurs now in less than 10% of patients. Unlike the spondyloarthritides, RA rarely affects the thoracic and lumbar spine. Radiographic abnormalities of the temporomandibular joint occur commonly in patients with RA, but they are generally not associated with significant symptoms or functional impairment.

Extraarticular manifestations may develop during the clinical course of RA, even prior to the onset of arthritis **(Fig. 6-2)**. Patients most likely to develop extraarticular disease have a history of smoking, have early onset of significant physical disability, and test positive for serum RF. Subcutaneous nodules, secondary Sjögren's syndrome, pulmonary nodules, and anemia are among the most frequently observed extraarticular manifestations. Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty's syndrome and vasculitis.

The most common systemic and extraarticular features of RA are described in more detail in the sections below.

CONSTITUTIONAL

These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia; they generally reflect a high degree of inflammation and may even precede the onset of joint symptoms. In general, the presence of a fever of >38.3°C (101°F) at any time during the clinical course should raise suspicion of systemic vasculitis (see below) or infection.

NODULES

Subcutaneous nodules occur in 30–40% of patients and more commonly in those with the highest levels of disease activity, the disease-related shared epitope (see below), a positive test for serum RF, and radiographic evidence of joint erosions. When palpated, the nodules are generally firm; nontender; and adherent to periosteum, tendons, or bursae; developing in areas of the skeleton subject to repeated trauma or irritation such as the forearm, sacral prominences, and Achilles tendon. They may also occur in the lungs, pleura, pericardium, and peritoneum. Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene.

SJÖGREN'S SYNDROME

Secondary Sjögren's syndrome **(Chap. 9)** is defined by the presence of either keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) in association with another connective tissue disease, such as RA. Approximately 10% of patients with RA have secondary Sjögren's syndrome.

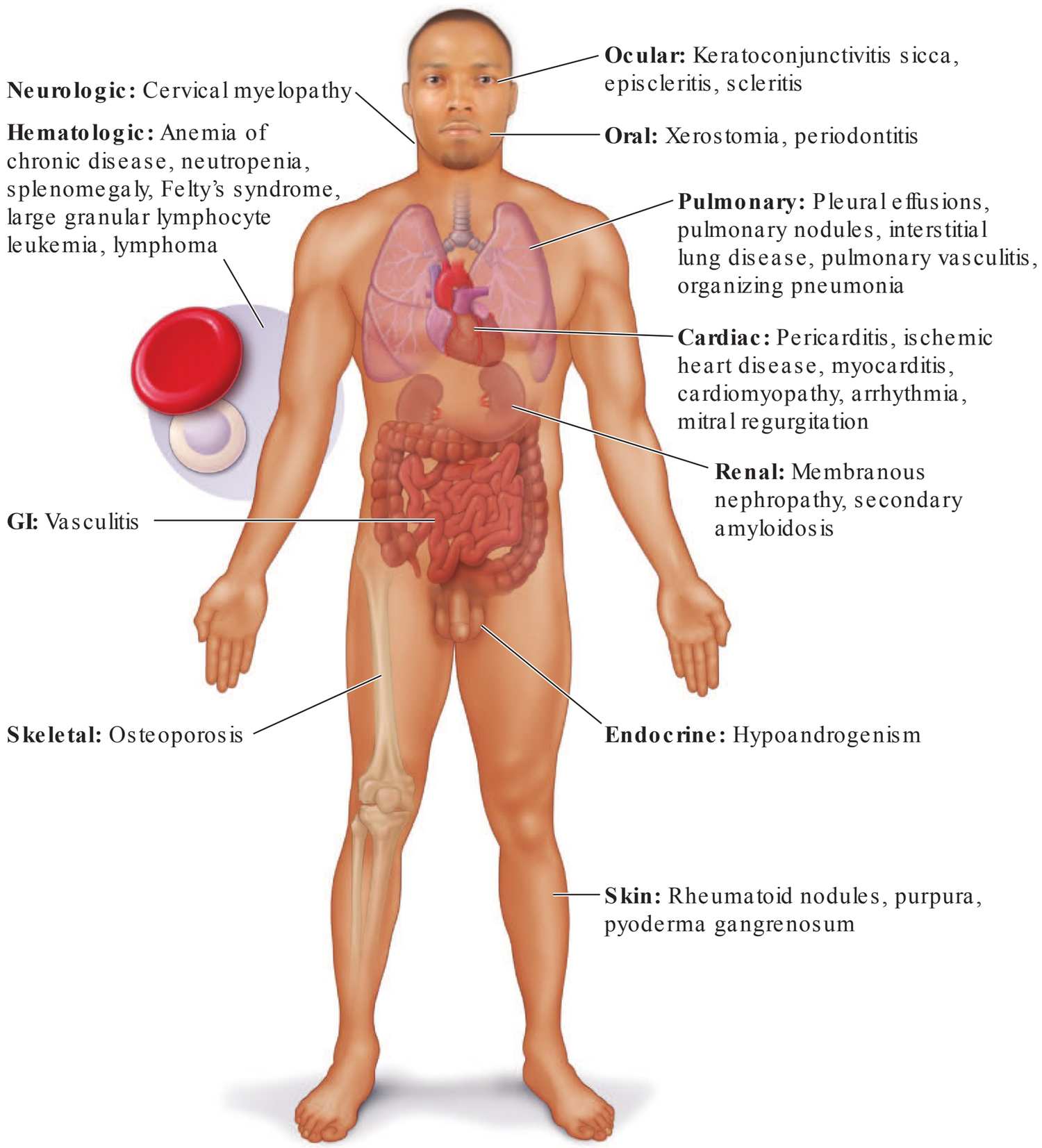


FIGURE 6-2
Extraarticular manifestations of rheumatoid arthritis.

PULMONARY

Pleuritis, the most common pulmonary manifestation of RA, may produce pleuritic chest pain and dyspnea, as well as a pleural friction rub and effusion. Pleural effusions tend to be exudative with increased numbers of monocytes and neutrophils. Interstitial lung disease (ILD) may also occur in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath. ILD can be associated with cigarette smoking and is generally found in patients with higher disease activity, although it may be diagnosed in up to 3.5% of patients prior to the onset of joint symptoms. Diagnosis is readily made by high-resolution chest computed tomography (CT) scan. Pulmonary function testing shows a restrictive pattern (e.g., reduced total lung capacity) with a reduced diffusing capacity for carbon monoxide (DL_{CO}). The presence of ILD confers a poor prognosis. The prognosis is not quite as poor as that of idiopathic pulmonary fibrosis (e.g., usual interstitial pneumonitis) because ILD secondary to RA responds more favorably than idiopathic ILD to immunosuppressive therapy. Pulmonary nodules may be solitary or multiple. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure. Other less common pulmonary findings include respiratory bronchiolitis and bronchiectasis.

CARDIAC

The most frequent site of cardiac involvement in RA is the pericardium. However, clinical manifestations of pericarditis occur in less than 10% of patients with RA despite the fact that pericardial involvement may be detected in nearly one-half of the these patients by

echocardiogram or autopsy studies. Cardiomyopathy, another clinically important manifestation of RA, may result from necrotizing or granulomatous myocarditis, coronary artery disease, or diastolic dysfunction. T is involvement too may be subclinical and only identified by echocardiography or cardiac magnetic resonance imaging (MRI). Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid. Mitral regurgitation is the most common valvular abnormality in RA, occurring at a higher frequency than the general population.

VASCULITIS

Rheumatoid vasculitis **(Chap. 11)** typically occurs in patients with long-standing disease, a positive test for serum RF, and hypocomplementemia. T e overall incidence has decreased significantly in the last decade to be less than 1% of patients. T e cutaneous signs vary and include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations. Vasculitic ulcers, which may be difficult to distinguish from those caused by venous insufficiency, may be treated successfully with immunosuppressive agents (requiring cytotoxic treatment in severe cases) as well as skin grafting. Sensorimotor polyneuropathies, such as mononeuritis multiplex, may occur in association with systemic rheumatoid vasculitis.

HEMATOLOGIC

A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality. T e degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Platelet counts may also be elevated in RA as an acute-phase reactant. Immune-mediated thrombocytopenia is rare in this disease.

Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in less than 1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. It typically occurs in the late stages of severe RA and is more common in whites than other racial groups. T cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty's syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often due to drug therapy.

LYMPHOMA

Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. T e most common histopathologic type of lymphoma is a diffuse large B cell lymphoma. T e risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

ASSOCIATED CONDITIONS

In addition to extraarticular manifestations, several conditions associated with RA contribute to disease morbidity and mortality rates. T ey are worthy of mention because they affect chronic disease management.

Cardiovascular disease

T e most common cause of death in patients with RA is cardiovascular disease. T e incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population. T e presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease in this population.

Osteoporosis

Osteoporosis is more common in patients with RA than an age- and sex-matched population, with prevalence rates of 20–30%. T e inflammatory milieu of the joint probably spills over into the rest of the body and promotes generalized bone loss by activating osteoclasts. Chronic use of glucocorticoids and disability-related immobility also contributes to osteoporosis. Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

Hypoandrogenism

Men and postmenopausal women with RA have lower mean serum testosterone, luteinizing hormone (LH), and dehydroepiandrosterone (DHEA) levels than control populations. It has thus been hypothesized that hypoandrogenism may play a role in the pathogenesis of RA or arise as a consequence of the chronic inflammatory response. It is also important to realize that patients receiving chronic glucocorticoid therapy may develop hypoandrogenism owing to inhibition of LH

and follicle-stimulating hormone (FSH) secretion from the pituitary gland. Because low testosterone levels may lead to osteoporosis, men with hypoandrogenism should be considered for androgen replacement therapy.

EPIDEMIOLOGY

RA affects approximately 0.5–1% of the adult population worldwide. T ere is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. T e incidence and prevalence of RA varies based on geographic location, both globally and among certain ethnic groups within a country **(Fig. 6-3)**. For example, the Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates for RA in the range of 0.2–0.4%.

Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of estrogen in disease pathogenesis. Most of the theories center on the role of estrogens in enhancing the immune response. For example, some experimental studies have shown that estrogen can stimulate production of tumor necrosis factor a (TNF-α), a major cytokine in the pathogenesis of RA.

GENETIC CONSIDERATIONS



It has been recognized for over 30 years that genetic factors contribute to the occurrence of RA as well as to its severity. T e likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population. T ere remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. Although twin studies imply that genetic factors may explain up to 60% of the occurrence of RA, the more commonly stated estimate falls in the range of 10–25%. T e estimate of genetic influence may vary across studies due to gene–environment interactions.

T e alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC). It has been estimated that one-third of the genetic risk for RA resides within this locus. Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β-chain molecule. T e disease-associated

European ancestry:
HLA-DRB1:
- *0401
- *0404
- *0301
- ***0101**

PTPN22: European
STAT4: North American
TNFAIP3: North American
TRAFI/CF: North American
CTLA4: European

Asian ancestry:
HLA-DRB1:
- *0401 (East Asian)
- *0405
- *0901 (Japanese, Malaysian, Korean)

PADI4
CD244

Other:
CD40

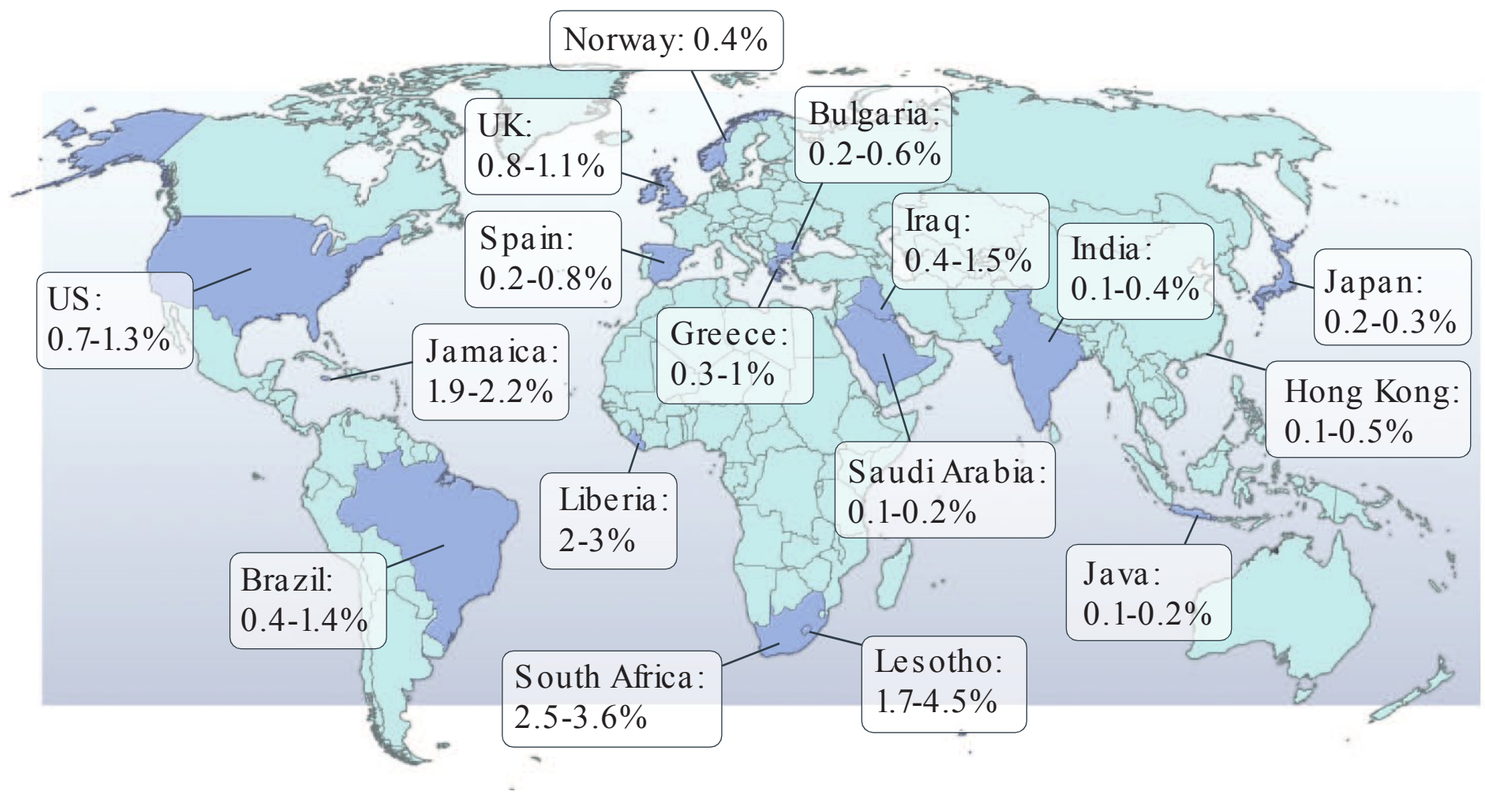


FIGURE 6-3
Global prevalence rates of rheumatoid arthritis (RA) with genetic associations. Listed are the major genetic alleles associated with RA. Although human leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been associated with RA in only certain ethnic groups.

HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β-chain, termed the shared epitope (SE). Carriership of the SE alleles is associated with production of anti-CCP antibodies and worse disease outcomes. Some of these HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, *0404, *1001, and *0901). Additionally, there is regional variation. In Greece, for example, where RA tends to be milder than in western European countries, RA susceptibility has been associated with the *0101 SE allele. By comparison, the *0401 or *0404 alleles are found in approximately 50–70% of northern Europeans and are the predominant risk alleles in this group. The most common disease susceptibility SE alleles in Asians, namely the Japanese, Koreans, and Chinese, are *0405 and *0901. Lastly, disease susceptibility of Native American populations such as the Pima and Tlingit Indians, where the prevalence of RA can be as high as 7%, is associated with the SE allele *1042. The risk of RA conferred by these SE alleles is less in African and Hispanic Americans than in individuals of European ancestry.

Genome-wide association studies (GWAS) have made possible the identification of several non-MHC-related genes that contribute to RA susceptibility. GWAS are based on the detection of single-nucleotide polymorphisms (SNPs), which allow for examination of the genetic architecture of complex diseases such as RA. There are approximately 10 million common SNPs within a human genome consisting of 3 billion base pairs. As a rule, GWAS identify only common variants, namely, those with a frequency of more than 5% in the general population.

Overall, several themes have emerged from GWAS in RA. First, the non-MHC loci identified as risk alleles for RA have only a modest effect on risk; they also contribute to the risk for developing other autoimmune diseases, such as type 1 diabetes mellitus, systemic lupus erythematosus, and multiple sclerosis. Second, although most of the non-HLA associations are described in patients with anti-CCP antibody-positive disease, there are several risk loci that are unique to anti-CCP antibody-negative disease. Third, risk alleles vary among ethnic groups. And fourth, the risk loci mostly reside in genes encoding proteins involved in the regulation of the immune response. However, the risk alleles identified by GWAS only account at present for approximately 5% of the genetic risk, suggesting that rare variants or other classes of DNA variants, such as variants in copy number, may be yet found that significantly contribute to the overall risk model.

Recently, imputation of SNP data from a GWAS meta-analysis shows amino acid substitutions in the MHC locus independently associated with the risk for RA are at position 11, 71, and 74 in HLA-DRβ1, position 9 of HLA-B, and position 9 of HLA-DPβ1. The amino acids at position 11, 71, and 74 are located in the antigen-binding grove of the HLA-DRβ1 molecule, highlighting positions 71 and 74 that form part of the original shared epitope.

Among the best examples of the non-MHC genes contributing to the risk of RA is the gene encoding protein tyrosine phosphatase non-receptor 22 (PTPN22). This gene varies in frequency among patients from different parts of Europe (e.g., 3–10%), but is absent in patients of East Asian ancestry. PTPN22 encodes lymphoid tyrosine phosphatase, a protein that regulates T and B cell function. Inheritance of the risk allele for PTPN22 produces a gain-of-function in the protein that is hypothesized to result in the abnormal thymic selection of autoreactive T and B cells and appears to be associated exclusively with anti-CCP-positive disease. The peptidyl arginine deiminase type IV (PADI4) gene is another risk allele that encodes an enzyme involved in the conversion of arginine to citrulline and is postulated to play a role in the development of antibodies to citrullinated antigens. A polymorphism in PADI4 has been associated with RA only in Asian populations.

Epigenetics is the study of heritable traits that affect gene expression but do not modify DNA sequence. It may provide a link between environmental exposure and predisposition to disease. The best-studied mechanisms include posttranslational histone modifications and DNA methylation. Although studies of epigenetic phenomena are limited, DNA methylation patterns have been shown to differ between RA patients and healthy controls, as well as patients with osteoarthritis.

ENVIRONMENTAL FACTORS

In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5. In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation. A twin who smokes will have a significantly higher risk for RA than his or her monozygotic co-twin, theoretically with the same genetic risk, who does not smoke. Interestingly, the risk from smoking is almost exclusively related to RF and anti-CCP antibody-positive disease. However, it has not been shown that smoking cessation, while having many health benefits, improves disease activity.

Researchers began to aggressively seek an infectious etiology for RA after the discovery in 1931 that sera

from patients with this disease could agglutinate strains of streptococci. Certain viruses such as Epstein-Barr virus (EBV) have garnered the most interest over the past 30 years given their ubiquity, ability to persist for many years in the host, and frequent association with arthritic complaints. For example, titers of IgG antibodies against EBV antigens in the peripheral blood and saliva are significantly higher in patients with RA than the general population. EBV DNA has also been found in synovial fluid and synovial cells of RA patients. Because the evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as a causative factor in RA.

PATHOLOGY

RA affects the synovial tissue and underlying cartilage and bone. T e synovial membrane, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue. In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage. It consists primarily of two cell types—type A synoviocytes (macrophage-derived) and type B synoviocytes (fibroblast-derived). T e synovial fibroblasts are the most abundant and produce the structural components of joints, including collagen, fibronectin, and laminin, as well as other extracellular constituents of the synovial matrix. T e sublining layer consists of blood vessels and a sparse population of mononuclear cells within a loose network of connective tissue. Synovial fluid, an ultrafiltrate of blood, diffuses through the subsynovial lining tissue across the synovial membrane and into the joint cavity. Its main constituents are hyaluronan and lubricin. Hyaluronan is a glycosaminoglycan that contributes to the viscous nature of synovial fluid, which along with lubricin, lubricates the surface of the articular cartilage.

T e pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane containing fibroblast-like synoviocytes and granulation-reactive fibrovascular tissue that invades the underlying cartilage and bone. T e inflammatory infiltrate is made up of no less than six cell types: T cells, B cells, plasma cells, dendritic cells, mast cells, and, to a lesser extent, granulocytes. T e T cells comprise 30–50% of the infiltrate, with the other cells accounting for the remainder. T e topographical organization of these cells is complex and may vary among individuals with RA. Most often, the lymphocytes are diffusely organized among the tissue resident cells; however, in some cases, the B cells, T cells, and dendritic cells may form higher levels of organization, such as lymphoid follicles and germinal center–like structures. Growth factors secreted by synovial fibroblasts and macrophages promote the formation of new blood vessels in the synovial sublining that supply the increasing demands for oxygenation and nutrition required by the infiltrating leukocytes and expanding synovial tissue.

T e structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast. Osteoclasts are multinucleated giant cells that can be identified by their expression of CD68, tartrate-resistant acid phosphatase, cathepsin K, and the calcitonin receptor. T ey appear at the pannus-bone interface where they eventually form resorption lacunae. T ese lesions typically localize where the synovial membrane inserts into the periosteal surface at the edges of bones close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths. T is process most likely explains why bone erosions usually develop at the radial sites of the MCP joints juxtaposed to the insertion sites of the tendons, collateral ligaments, and synovial membrane. Another form of bone loss is periarticular osteopenia that occurs in joints with active inflammation. It is associated with substantial thinning of the bony trabeculae along the metaphyses of bones, and likely results from inflammation of the bone marrow cavity. T ese lesions can be visualized on MRI scans, where they appear as signal alterations in the bone marrow adjacent to inflamed joints. T eir signal characteristics show they are water-rich with a low fat content and are consistent with highly vascularized inflammatory tissue. T ese bone marrow lesions are often the forerunner of bone erosions.

T e cortical bone layer that separates the bone marrow from the invading pannus is relatively thin and susceptible to penetration by the inflamed synovium. T e bone marrow lesions seen on MRI scans are associated with an endosteal bone response characterized by the accumulation of osteoblasts and deposition of osteoid. T us, in recent years, the concept of joint pathology in RA has been extended to include the bone marrow cavity. Finally, generalized osteoporosis, which results in the thinning of trabecular bone throughout the body, is a third form of bone loss found in patients with RA.

Articular cartilage is an avascular tissue comprised of a specialized matrix of collagens, proteoglycans, and other proteins. It is organized in four distinct regions (superficial, middle, deep, and calcified cartilage zones)—chondrocytes constitute the unique cellular component in these layers. Originally, cartilage was considered to be an inert tissue, but it is now known to be a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which in

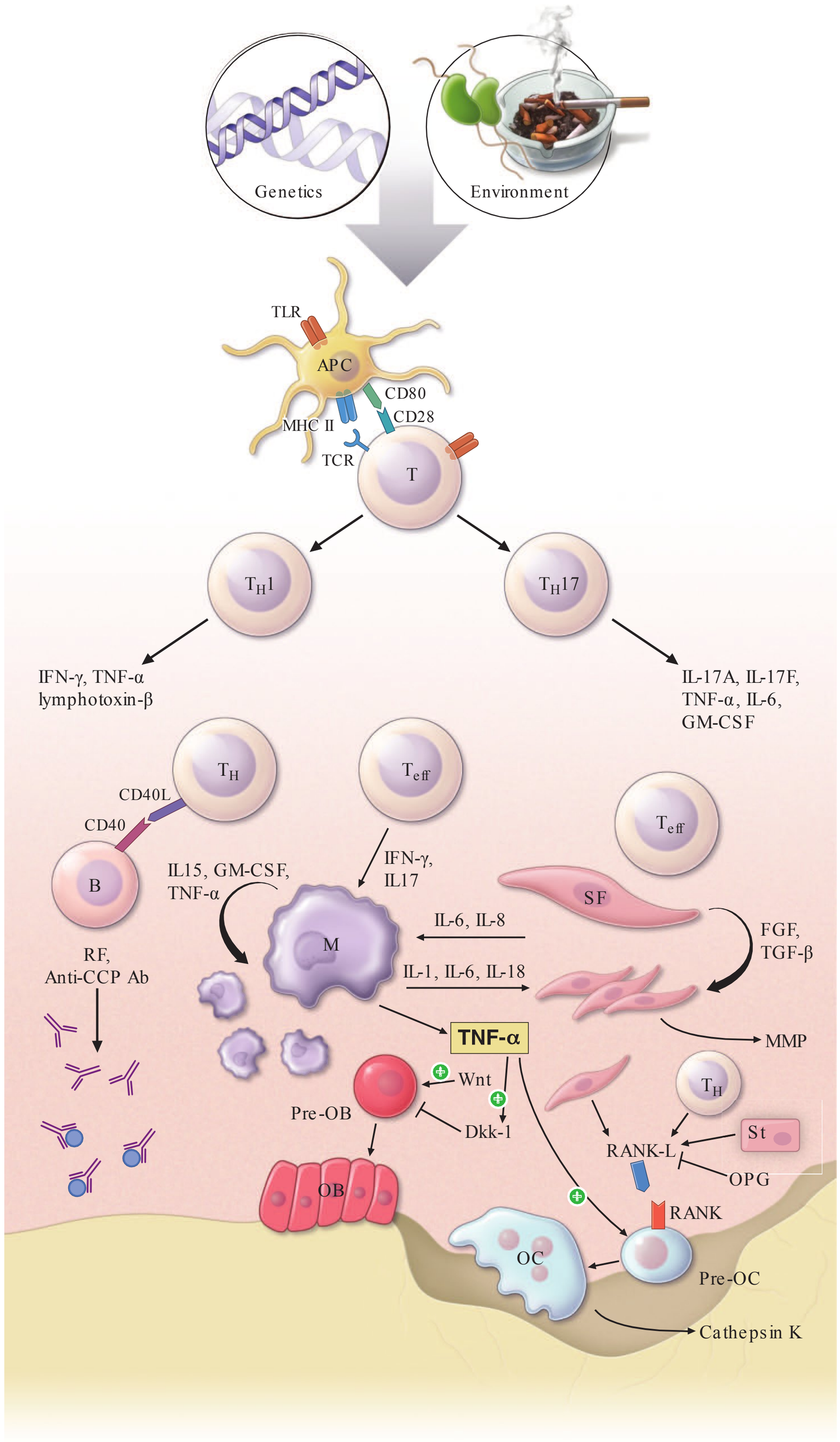


FIGURE 6-4

Pathophysiologic mechanisms of inflammation and joint destruction. Genetic predisposition along with environmental factors may trigger the development of rheumatoid arthritis (RA), with subsequent synovial T cell activation. CD4+ T cells become activated by antigen-presenting cells (APCs) through interactions between the T cell receptor and class II major histocompatibility complex (MHC)-peptide antigen (signal 1) with co-stimulation through the CD28-CD80/86 pathway, as well as other pathways

turn, alter the balance between cartilage anabolism and catabolism. In RA, the initial areas of cartilage degradation are juxtaposed to the synovial pannus. T e cartilage matrix is characterized by a generalized loss of proteoglycan, most evident in the superficial zones adjacent to the synovial fluid. Degradation of cartilage may also take place in the perichondrocytic zone and in regions adjacent to the subchondral bone.

PATHOGENESIS

T e pathogenic mechanisms of synovial inflammation are likely to result from a complex interplay of genetic, environmental, and immunologic factors that produces dysregulation of the immune system and a breakdown in self-tolerance **(Fig. 6-4)**. Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune system remains a mystery. However, a detailed molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the destruction of the articular cartilage and bone.

In RA, the preclinical stage appears to be characterized by a breakdown in self-tolerance. T is idea is supported by the finding that autoantibodies, such as RF and anti-CCP antibodies, may be found in sera from patients many years before clinical disease can be detected. However, the antigenic targets of anti-CCP antibodies and RF are not restricted to the joint, and their role in disease pathogenesis remains speculative. Anti-CCP antibodies are directed against deaminated peptides, which result from posttranslational modification by the enzyme PADI4. T ey recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen, and vimentin, and are present at higher levels in the joint fluid compared to the serum. Other autoantibodies have been found in a minority of patients with RA, but they also occur in the setting of other types of arthritis. T ey bind to a diverse array of autoantigens, including type II collagen, human cartilage gp-39, aggrecan, calpastatin, BiP (immunoglobulin binding protein), and glucose-6-phosphate isomerase.

In theory, environmental stimulants may synergize with other factors to bring about inflammation in RA. People who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke. T us, it has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins in the lung and stimulate the expression of a neoepitope capable of inducing self-reactivity, which in turns, leads to formation of immune complexes and joint inflammation. Exposure to silicone dust and mineral oil, which has adjuvant effects, has also been linked to an increased risk for anti-CCP antibody-positive RA.

How might microbes or their products be involved in the initiating events of RA? T e immune system is alerted to the presence of microbial infections through Toll-like receptors (TLRs). T ere are 10 TLRs in humans that recognize a variety of microbial products, including bacterial cell-surface lipopolysaccharides and heat-shock proteins (TLR4), lipoproteins (TLR2), double-strand RNA viruses (TLR3), and unmethylated CpG DNA from bacteria (TLR9). TLR2, -3, and -4 are abundantly expressed by synovial fibroblasts in early RA and, when bound by their ligands, upregulate production of proinflammatory cytokines. Although such events could amplify inflammatory pathways in RA, a

(signal 2). In theory, ligands binding Toll-like receptors (TLRs) may further stimulate activation of APCs inside the joint. Synovial CD4+ T cells differentiate into T_H1 and T_H17 cells, each with their distinctive cytokine profile. CD4+ T_H cells in turn activate B cells, some of which are destined to differentiate into autoantibody-producing plasma cells. Immune complexes, possibly comprised of rheumatoid factors (RFs) and anti–cyclic citrullinated peptides (CCP) antibodies, may form inside the joint, activating the complement pathway and amplifying inf ammation. T effector cells stimulate synovial macrophages (M) and fibroblasts (SF) to secrete proinf ammatory mediators, among which is tumor necrosis factor α (TNF-α). TNF-α upregulates adhesion molecules on endothelial cells, promoting leukocyte inf ux into the joint. It also stimulates the production of other inf ammatory mediators, such as interleukin 1 (IL-1), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). TNF-α has a critically important function in regulating the balance between bone destruction and formation. It upregulates the expression of dickkopf-1 (DKK-1), which can then internalize Wnt receptors on osteoblast precursors. Wnt is a soluble mediator that promotes osteoblastogenesis and bone formation. In RA, bone formation is inhibited through the Wnt pathway, presumably due to the action of elevated levels of DKK-1. In addition to inhibiting bone formation, TNF-α stimulates osteoclastogenesis. However, it is not sufficient by itself to induce the differentiation of osteoclast precursors (Pre-OC) into activated osteoclasts capable of eroding bone. Osteoclast differentiation requires the presence of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which binds to RANK on the surface of Pre-OC. Inside the joint, RANKL is mainly derived from stromal cells, synovial fibroblasts, and T cells. Osteoprotegerin (OPG) acts as a decoy receptor for RANKL, thereby inhibiting osteoclastogenesis and bone loss. FGF, fibroblast growth factor; IFN, interferon; TGF, transforming growth factor.

specific role for TLRs in disease pathogenesis has not been elucidated.

The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response. In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection due to defects in DNA repair leading to an imbalance of T cell death and life, or defects in the cell signaling apparatus lowering the threshold for T cell activation. Similarly, abnormal selection of the T cell repertoire in the periphery might lead to a breakdown in T cell tolerance. The support for these theories comes mainly from studies of arthritis in mouse models. It has not been shown that patients with RA have abnormal thymic selection of T cells or defective apoptotic pathways regulating cell death. At least some antigen stimulation inside the joint seems likely, owing to the fact that T cells in the synovium express a cell-surface phenotype indicating prior antigen exposure and show evidence of clonal expansion. Of interest, peripheral blood T cells from patients with RA have been shown to display a fingerprint of premature aging that mostly affects inexperienced naïve T cells. In these studies, the most glaring findings have been the loss of telomeric sequences and a decrease in the thymic output of new T cells. Although intriguing, it is not clear how generalized T cell abnormalities might provoke a systemic disease dominated by synovitis.

There is substantial evidence supporting a role for CD4+ T cells in the pathogenesis of RA. First, the coreceptor CD4 on the surface of T cells binds to invariant sites on MHC class II molecules, stabilizing the MHC-peptide–T cell receptor complex during T cell activation. Because the SE on MHC class II molecules is a risk factor for RA, it follows that CD4+ T cell activation may play a role in the pathogenesis of this disease. Second, CD4+ memory T cells are enriched in the synovial tissue from patients with RA and can be implicated through "guilt by association." Third, CD4+ T cells have been shown to be important in the initiation of arthritis in animal models. Fourth, some, but not all, T cell–directed therapies have shown clinical efficacy in this disease. Taken together, these lines of evidence suggest that CD4+ T cells play an important role in orchestrating the chronic inflammatory response in RA. However, other cell types, such as CD8+ T cells, natural killer (NK) cells, and B cells are present in synovial tissue and may also influence pathogenic responses.

In the rheumatoid joint, by mechanisms of cell-cell contact and release of soluble mediators, activated T cells stimulate macrophages and fibroblast-like synoviocytes to generate proinflammatory mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone. CD4+ T cell activation is dependent on two signals: (1) T cell receptor binding to peptide-MHC on antigen-presenting cells; and (2) CD28 binding to CD80/86 on antigen-presenting cells. CD4+ T cells also provide help to B cells, which in turn, produce antibodies that may promote further inflammation in the joint. The previous T cell–centric model for the pathogenesis of RA was based on a T_H1-driven paradigm, which came from studies indicating that CD4+ T helper (T_H) cells differentiated into T_H1 and T_H2 subsets, each with their distinctive cytokine profiles. T_H1 cells were found to mainly produce interferon γ (IFN-γ), lymphotoxin β, and TNF-α, whereas T_H2 cells predominately secreted interleukin (IL)-4, IL-5, IL-6, IL-10, and IL-13. The recent discovery of another subset of T_H cells, namely the T_H17 lineage, has revolutionized our concepts concerning the pathogenesis of RA. In humans, naïve T cells are induced to differentiate into T_H17 cells by exposure to transforming growth factor β (TGF-β), IL-1, IL-6, and IL-23. Upon activation, T_H17 cells secrete a variety of proinflammatory mediators such as IL-17, IL-21, IL-22, TNF-α, IL-26, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Substantial evidence now exists from both animal models and humans that IL-17 plays an important role not only in promoting joint inflammation, but also in destroying cartilage and subchondral bone.

The immune system has evolved mechanisms to counterbalance the potential harmful immune-mediated inflammatory responses provoked by infectious agents and other triggers. Among these negative regulators are regulatory T (T_{reg}) cells, which are produced in the thymus and induced in the periphery to suppress immune-mediated inflammation. They are characterized by the surface expression of CD25 and the transcription factor forkhead box P3 (FOXP3) and orchestrate dominant tolerance through contact with other immune cells and secretion of inhibitory cytokines, such as TGF-β, IL-10, and IL-35. T_{reg} cells appear to be heterogeneous and capable of suppressing distinct classes (T_H1, T_H2, T_H17) of the immune response. In RA, the data that T_{reg} numbers are deficient compared to normal healthy controls are contradictory and inconclusive. Although some experimental evidence suggests that T_{reg} suppressive activity is lost due to dysfunctional expression of cytotoxic T lymphocyte antigen 4 (CTLA-4), the nature of T_{reg} defects in RA, if they exist, remains unclear.

Cytokines, chemokines, antibodies, and endogenous danger signals bind to receptors on the surface of immune cells and stimulate a cascade of intracellular signaling events that can amplify the inflammatory response. Signaling molecules and their binding partners in these pathways are the target of small-molecule drugs designed to interfere with signal transduction and block these reinforcing inflammatory loops. Examples

of signal molecules in these critical inflammatory pathways include Janus kinase (JAK)/signal transducers and activators of transcription (STAT), spleen tyrosine kinase (Syk), mitogen-activated protein kinases (MAPKs), and nuclear factor-κB (NF-κB). T ese pathways exhibit significant cross-talk and are found in many cell types. Some signal transducers, such as JAK3, are primarily expressed in hematopoietic cells and play an important role in the inflammatory response in RA.

Activated B cells are also important players in the chronic inflammatory response. B cells give rise to plasma cells, which in turn, produce antibodies, including RF and anti-CCP antibodies. RFs may form large immune complexes inside the joint that contribute to the pathogenic process by fixing complement and promoting the release of proinflammatory chemokines and chemoattractants. In mouse models of arthritis, RF-containing immune complexes and anti-CCP-containing immune complexes synergize with other mechanisms to exacerbate the synovial inflammatory response.

RA is often considered to be a macrophage-driven disease because this cell type is the predominant source of proinflammatory cytokines inside the joint. Key proinflammatory cytokines released by synovial macrophages include TNF-α, IL-1, IL-6, IL-12, IL-15, IL-18, and IL-23. Synovial fibroblasts, the other major cell type in this microenvironment, produce the cytokines IL-1 and IL-6 as well as TNF-α. TNF-α is a pivotal cytokine in the pathobiology of synovial inflammation. It upregulates adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment; activates synovial fibroblasts; stimulates angiogenesis; promotes pain receptor sensitizing pathways; and drives osteoclastogenesis. Fibroblasts secrete matrix metalloproteinases (MMPs) as well as other proteases that are chiefly responsible for the breakdown of articular cartilage.

Osteoclast activation at the site of the pannus is closely tied to the presence of focal bone erosion. Receptor activator of nuclear factor-κB ligand (RANKL) is expressed by stromal cells, synovial fibroblasts, and T cells. Upon binding to its receptor RANK on osteoclast progenitors, RANKL stimulates osteoclast differentiation and bone resorption. RANKL activity is regulated by osteoprotegerin (OPG), a decoy receptor of RANKL that blocks osteoclast formation. Monocytic cells in the synovium serve as the precursors of osteoclasts and, when exposed to macrophage colony-stimulating factor (M-CSF) and RANKL, fuse to form polykaryons termed preosteoclasts. T ese precursor cells undergo further differentiation into osteoclasts with the characteristic ruf ed membrane. Cytokines such as TNF-α, IL-1, IL-6, and IL-17 increase the expression of RANKL in the joint and thus promote osteoclastogenesis. Osteoclasts also secrete cathepsin K, which is a cysteine protease that degrades the bone matrix by cleaving collagen. Stimulation of osteoclasts also contributes to generalized bone loss and osteoporosis.

Increased bone loss is only part of the story in RA, as decreased bone formation plays a crucial role in bone remodeling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. T e proinflammatory cytokine TNF-α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1). DKK-1 is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation. T e Wnt system is a family of soluble glycoproteins that bind to cell-surface receptors known as frizzled (fz) and low-density lipoprotein (LDL) receptor–related proteins (LRPs) and promote cell growth. In animal models, increased levels of DKK-1 are associated with decreased bone formation, whereas inhibition of DKK-1 protects against structural damage in the joint. Wnt proteins also induce the formation of OPG and thereby shut down bone resorption, emphasizing their key role in tightly regulating the balance between bone resorption and formation.

DIAGNOSIS

T e clinical diagnosis of RA is largely based on signs and symptoms of a chronic inflammatory arthritis, with laboratory and radiographic results providing important supplemental information. In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy **(Table 6-1)**. Application of the newly revised criteria yields a score of 0–10, with a score of ≥ 6 fulfilling the requirements for definite RA. T e new classification criteria differ in several ways from the older criteria set. T e new criteria include a positive test for serum anti-CCP antibodies (also termed ACPA, anti-citrullinated peptide antibodies) as an item, which carries greater specificity for the diagnosis of RA than a positive test for RF. T e newer classification criteria also do not take into account whether the patient has rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA. It is important to emphasize that the new 2010 ACR-EULAR criteria are "classification criteria" as opposed to "diagnostic criteria" and serve to distinguish patients at the onset of disease who have a high likelihood of evolution to chronic disease

TABLE 6-1

CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

		SCORE
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (≤3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of ≥6 fulfills requirements for definite RA.

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal.

Source: D Aletaha et al: Arthritis Rheum 62:2569, 2010.

with persistent synovitis and joint damage. The presence of radiographic joint erosions or subcutaneous nodules may inform the diagnosis in the later stages of the disease.

LABORATORY FEATURES

Patients with systemic inflammatory diseases such as RA will often present with elevated nonspecific inflammatory markers such as an ESR or CRP. Detection of serum RF and anti-CCP antibodies is important in differentiating RA from other polyarticular diseases, although RF lacks diagnostic specificity and may be found in association with other chronic inflammatory diseases in which arthritis figures in the clinical manifestations.

IgM, IgG, and IgA isotypes of RF occur in sera from patients with RA, although the IgM isotype is the one most frequently measured by commercial laboratories. Serum IgM RF has been found in 75–80% of patients with RA; therefore, a negative result does not exclude the presence of this disease. It is also found in other connective tissue diseases, such as primary Sjögren's syndrome, systemic lupus erythematosus, and type II mixed essential cryoglobulinemia, as well as chronic infections such as subacute bacterial endocarditis and hepatitis B and C. Serum RF may also be detected in 1–5% of the healthy population.

The presence of serum anti-CCP antibodies has about the same sensitivity as serum RF for the diagnosis of RA. However, its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of an early inflammatory arthritis is useful for distinguishing RA from other forms of arthritis. There is some incremental value in testing for the presence of both RF and anti-CCP, as some patients with RA are positive for RF but negative for anti-CCP and visa versa. The presence of RF or anti-CCP antibodies also has prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes.

SYNOVIAL FLUID ANALYSIS

Typically, synovial fluid from patients with RA reflects an inflammatory state. Synovial fluid white blood cell (WBC) counts can vary widely, but generally range between 5000 and 50,000 WBC/μL compared to <2000 WBC/μL for a noninflammatory condition such as osteoarthritis. In contrast to the synovial tissue, the overwhelming cell type in the synovial fluid is the neutrophil. Clinically, the analysis of synovial fluid is most useful for confirming an inflammatory arthritis (as opposed to osteoarthritis), while at the same time excluding infection or a crystal-induced arthritis such as gout or pseudogout **(Chap. 20)**.

JOINT IMAGING

Joint imaging is a valuable tool not only for diagnosing RA, but also for tracking progression of any joint damage. Plain x-ray is the most common imaging modality, but it is limited to visualization of the bony structures and inferences about the state of the articular cartilage based on the amount of narrowing of the joint space. MRI and ultrasound techniques offer the added value of detecting changes in the soft tissues such as synovitis, tenosynovitis, and effusions as well as greater sensitivity for identifying bony abnormalities. Plain radiographs are usually relied upon in clinical practice for the purpose of diagnosis and monitoring of affected joints. However, in selected cases, MRI and ultrasound can provide additional diagnostic information that may guide clinical decision making. Musculoskeletal ultrasound with power Doppler is increasingly used in rheumatology clinical practice for detecting synovitis and bone erosion.

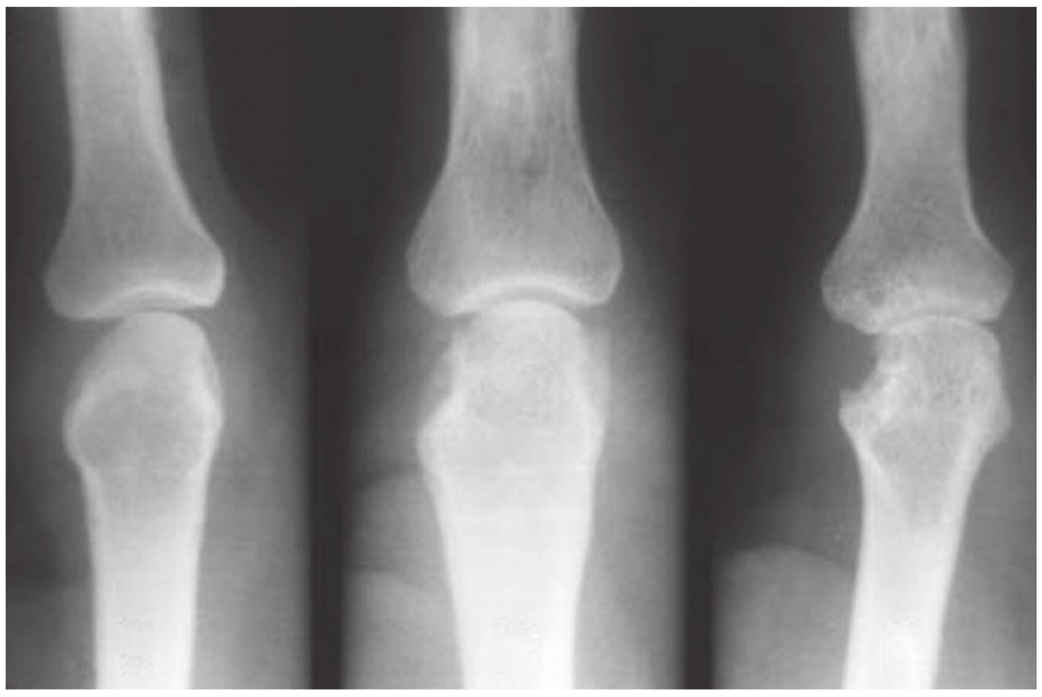


FIGURE 6-5
X-ray demonstrating progression of erosions on the proximal interphalangeal joint. (Courtesy of the American College of Rheumatology.)

Plain radiography

Classically in RA, the initial radiographic finding is periarticular osteopenia. Practically speaking, however, this finding is difficult to appreciate on plain films and, in particular, on the newer digitalized x-rays. Other findings on plain radiographs include soft tissue swelling, symmetric joint space loss, and subchondral erosions, most frequently in the wrists and hands (MCPs and PIPs) and the feet (MTPs). In the feet, the lateral aspect of the fifth MTP is often targeted first, but other MTP joints may be involved at the same time. X-ray imaging of advanced RA may reveal signs of severe destruction, including joint subluxation and collapse **(Fig. 6-5)**.

MRI

MRI offers the greatest sensitivity for detecting synovitis and joint effusions, as well as early bone and bone marrow changes. These soft tissue abnormalities often occur before osseous changes are noted on x-ray. Presence of bone marrow edema has been recognized to be an early sign of inflammatory joint disease and can predict the subsequent development of erosions on plain radiographs as well as MRI scans. Cost and availability of MRI are the main factors limiting its routine clinical use.

Ultrasound

Ultrasound, including power color Doppler, has the ability to detect more erosions than plain radiography, especially in easily accessible joints. It can also reliably detect synovitis, including increased joint vascularity indicative of inflammation. The usefulness of ultrasound is dependent on the experience of the sonographer; however, it does offer the advantages of portability, lack of radiation, and low expense relative to MRI, factors that make it attractive as a clinical tool.

CLINICAL COURSE

The natural history of RA is complex and affected by a number of factors including age of onset, gender, genotype, phenotype (i.e., extraarticular manifestations or variants of RA), and comorbid conditions, which make for a truly heterogeneous disease. There is no simple way to predict the clinical course. It is important to realize that as many as 10% of patients with inflammatory arthritis fulfilling ACR classification criteria for RA will undergo a spontaneous remission within 6 months (particularly seronegative patients). However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time. A minority of patients will show intermittent and recurrent explosive attacks of inflammatory arthritis interspersed with periods of disease quiescence. Finally, an aggressive form of RA may occur in an unfortunate few with inexorable progression of severe erosive joint disease, although this highly destructive course is less common in the modern treatment era of biologics.

Disability, as measured by the Health Assessment Questionnaire (HAQ), shows gradual worsening of disability over time in the face of poorly controlled disease activity and disease progression. Disability may result from both a disease activity–related component that is potentially reversible with therapy and a joint damage–related component owing to the cumulative and largely irreversible effects of cartilage and bone breakdown. Early in the course of disease, the extent of joint inflammation is the primary determinant of disability, while in the later stages of disease, the amount of joint damage is the dominant contributing factor. Previous studies have shown that more than one-half of patients with RA are unable to work 10 years after the onset of their disease; however, increased employability and less work absenteeism has been reported recently with the use of newer therapies and earlier treatment intervention.

The overall mortality rate in RA is two times greater than the general population, with ischemic heart disease being the most common cause of death followed by infection. Median life expectancy is shortened by an average of 7 years for men and 3 years for women compared to control populations. Patients at higher risk for shortened survival are those with systemic extraarticular involvement, low functional capacity, low socioeconomic status, low education, and chronic prednisone use.

TREATMENT Rheumatoid Arthritis

The amount of clinical disease activity in patients with RA reflects the overall burden of inflammation and is the variable most influencing treatment decisions. Joint inflammation is the main driver of joint damage and is the most important cause of functional disability in the early stages of disease. Several composite indices have been developed to assess clinical disease activity. The ACR 20, 50, and 70 improvement criteria (which corresponds to a 20%, 50%, and 70% improvement, respectively, in joint counts, physician/patient assessment of disease severity, pain scale, serum levels of acute-phase reactants [ESR or CRP], and a functional assessment of disability using a self-administered patient questionnaire) are a composite index with a dichotomous response variable. The ACR improvement criteria are commonly used in clinical trials as an endpoint for comparing the proportion of responders between treatment groups. In contrast, the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) are continuous measures of disease activity. These scales are increasingly used in clinical practice for tracking disease status and, in particular, for documenting treatment response.

Several developments during the past two decades have changed the therapeutic landscape in RA. They include (1) the emergence of methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone. The medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional DMARDs; and biologic DMARDs **(Table 6-2)**. Although disease for some patients with RA is managed adequately with a single DMARD, such as methotrexate, the situation in most cases demands the use of a combination DMARD regimen that may vary in its components over the treatment course depending on fluctuations in disease activity and emergence of drug-related toxicities and comorbidities.

NSAIDs NSAIDs were formerly viewed as the core of all other RA therapy, but they are now considered to be adjunctive therapy for management of symptoms uncontrolled by other measures. NSAIDs exhibit both analgesic and anti-inflammatory properties. The anti-inflammatory effects of NSAIDs derive from their ability to nonselectively inhibit cyclooxygenase (COX)-1 and COX-2. Although the results of clinical trials suggest NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

GLUCOCORTICOIDS Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1- to 2-week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5–10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy. Low-dose prednisone therapy has been shown in prospective studies to retard radiographic progression of joint disease; however, the benefits of this approach must be carefully weighed against the risks. Best practices minimize chronic use of low-dose prednisone therapy owing to the risk of osteoporosis and other long-term complications; however, the use of chronic prednisone therapy is unavoidable in many cases. High-dose glucocorticoids may be necessary for treatment of severe extraarticular manifestations of RA, such as ILD. Finally, if a patient exhibits one or a few actively inflamed joints, the clinician may consider intraarticular injection of an intermediate-acting glucocorticoid such as triamcinolone acetonide. This approach may allow for rapid control of inflammation in the setting of a limited number of affected joints. Caution must be exercised to appropriately exclude joint infection, as it often mimics an RA flare.

Osteoporosis ranks as an important long-term complication of chronic prednisone use. The ACR recommends risk stratifying patients based on clinical risk factors and/or the Fracture Risk Assessment Tool (FRAX) score. IF appropriate, a bisphosphonate should be started for glucocorticoid induced osteoporosis prevention. Although prednisone use is known to increase the risk of peptic ulcer disease, especially with concomitant NSAID use, no evidence-based guidelines have been published regarding the use of gastrointestinal ulcer prophylaxis in this situation.

DMARDs DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of approximately 6–12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. It was approved for the treatment of RA in 1986 and remains the benchmark for the efficacy and safety of new disease-modifying therapies. At the dosages used for the treatment of RA, methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. The clinical efficacy of leflunomide, an inhibitor of pyrimidine synthesis, appears similar to that of methotrexate; it has been shown in well-designed trials to be effective for the treatment of RA as monotherapy or in combination with methotrexate and other DMARDs.

Although similar to the other DMARDs in its slow onset of action, hydroxychloroquine has not been shown to delay

TABLE 6-2

DMARDS USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Hydroxychloroquine	200–400 mg/d orally (≤6.5 mg/kg)	Irreversible retinal damage Cardiotoxicity Blood dyscrasia	Nausea Diarrhea Headache Rash	Eye examination if >40 years old or prior ocular disease	Funduscopic and visual field testing every 12 months
Sulfasalazine	Initial: 500 mg orally twice daily Maintenance: 1000–1500 mg twice daily	Granulocytopenia Hemolytic anemia (with G6PD deficiency)	Nausea Diarrhea Headache	CBC, LFTs G6PD level	CBC every 2–4 weeks for first 3 months, then every 3 months
Methotrexate	10–25 mg/week orally or SQ Folic acid 1 mg/d to reduce toxicities	Hepatotoxicity Myelosuppression Infection Interstitial pneumonitis Pregnancy category X	Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue	CBC, LFTs Viral hepatitis panel[a] Chest x-ray	CBC, creatinine, LFTs every 2–3 months
Leflunomide	10–20 mg/d	Hepatotoxicity Myelosuppression Infection Pregnancy category X	Alopecia Diarrhea	CBC, LFTs Viral hepatitis panel[a]	CBC, creatinine, LFTs every 2–3 months
TNF-α Inhibitors	Infliximab: 3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks. May increase dose up to 10 mg/kg every 4 weeks	↑ Risk bacterial, fungal infections Reactivation of latent TB ↑ Lymphoma risk (controversial) Drug-induced lupus Neurologic deficits	Infusion reaction ↑ LFTs	PPD skin test	LFTs periodically
	Etanercept: 50 mg SQ weekly, or 25 mg SQ biweekly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Adalimumab: 40 mg SQ every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Golimumab: 50 mg SQ monthly	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
	Certolizumab: 400 mg SQ weeks 0, 2, 4, then 200 mg every other week	As above	Injection site reaction	PPD skin test	Monitor for injection site reactions
Abatacept	Weight based: <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1000 mg IV dose at weeks 0, 2, and 4, and then every 4 weeks OR 125 mg SQ weekly	↑ Risk bacterial, viral infections	Headache Nausea	PPD skin test	Monitor for infusion reactions

(continued)

TABLE 6-2

DMARDS USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (CONTINUED)

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Anakinra	100 mg SQ daily	↑ Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	PPD skin test CBC with differential	CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions
Rituximab	1000 mg IV × 2, days 0 and 14 May repeat course every 24 weeks or more Premedicate with methyl-prednisolone 100 mg to decrease infusion reaction	↑ Risk bacterial, viral infections Infusion reaction Cytopenia Hepatitis B reactivation	Rash Fever	CBC Viral hepatitis panel[a]	CBC at regular intervals
Tocilizumab	4–8 mg/kg 4–8 mg/kg IV monthly OR 162 mg SQ every other week (<100 kg weight) 162 mg SQ every week (≥100 kg weight)	Risk of infection Infusion reaction LFT elevation Dyslipidemia Cytopenias		PPD skin test	CBC and LFTs at regular intervals
Tofacitinib	5 mg orally twice daily or 11 mg XR once daily	Risk of infection LFT elevation Dyslipidemia Neutropenia	Upper respiratory tract infections Diarrhea Headache Nasopharyngitis	PPD skin test	CBC, LFTs, and lipids at regular intervals

[a]Viral hepatitis panel: hepatitis B surface antigen, hepatitis C viral antibody.
Abbreviations: CBC, complete blood count; DMARDs, disease-modifying antirheumatic drugs; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; LFTs, liver function tests; PPD, purified protein derivative; SQ, subcutaneous; TB, tuberculosis.

radiographic progression of disease and thus is not considered to be a true DMARD. In clinical practice, hydroxychloroquine is generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs. Sulfasalazine is used in a similar manner and has been shown in randomized, controlled trials to reduce radiographic progression of disease. Minocycline, gold salts, penicillamine, azathioprine, and cyclosporine have all been used for the treatment of RA with varying degrees of success; however, they are used sparingly now due to their inconsistent clinical efficacy or unfavorable toxicity profile.

BIOLOGICALS Biologic DMARDs have revolutionized the treatment of RA over the past decade (Table 6-2). They are protein therapeutics designed mostly to target cytokines and cell-surface molecules. The TNF inhibitors were the first biologicals approved for the treatment of RA. Anakinra, an IL-1 receptor antagonist, was approved shortly thereafter; however, its benefits have proved to be relatively modest compared with the other biologicals and is rarely used for the treatment of RA with the availability of other more effective agents. Abatacept, rituximab, and tocilizumab are the newest members of this class.

Anti-TNF Agents The development of TNF inhibitors was originally spurred by the experimental finding that TNF is a critical upstream mediator of joint inflammation. Currently, five agents that inhibit TNF-α are approved for the treatment of RA. There are three different anti-TNF monoclonal antibodies. Infliximab is a chimeric (part mouse and human) monoclonal antibody, whereas adalimumab and golimumab are humanized monoclonal antibodies. Certolizumab pegol is a pegylated Fc-free fragment of a humanized monoclonal antibody with binding specificity for TNF-α. Lastly, etanercept is a soluble fusion protein comprising the TNF receptor 2 in covalent linkage with the Fc portion of IgG1. All of the TNF inhibitors have

been shown in randomized controlled clinical trials to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs are typically used in combination with background methotrexate therapy. T is combination regimen, which affords maximal benefit in many cases, is often the next step for treatment of patients with an inadequate response to methotrexate therapy. Etanercept, adalimumab, certolizumab pegol, and golimumab have also been approved for use as monotherapy.

Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents and are contraindicated in patients with chronic hepatitis B infection or class III/IV congestive heart failure. T e major concern is the increased risk for infection, including serious bacterial infections, opportunistic fungal infection, and reactivation of latent tuberculosis. For this reason, all patients are screened for latent tuberculosis according to national guidelines prior to starting anti-TNF therapy. In the United States, patients are skin tested using an intradermal injection of purified protein derivative (PPD); individuals with skin reactions of more than 5 mm are presumed to have had previous exposure to tuberculosis and are evaluated for active disease and treated accordingly. T e QuantiFERON IFN-γ release assay may also be used in selected circumstances to screen for previous exposure to tuberculosis.

Anakinra Anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist. Although anakinra has seen limited use for the treatment of RA, it has enjoyed a resurgence of late as an effective therapy of some rare inherited syndromes dependent on IL-1 production, including neonatal-onset inflammatory disease, Muckle-Wells syndrome, and familial cold urticaria, as well as systemic juvenile-onset inflammatory arthritis and adult-onset Still's disease. Anakinra should not be combined with an anti-TNF drug due to the high rate of serious infections as observed with this regimen in a clinical trial.

Abatacept Abatacept is a soluble fusion protein consisting of the extracellular domain of human CTLA-4 linked to the modified portion of human IgG. It inhibits the co-stimulation of T cells by blocking CD28-CD80/86 interactions and may also inhibit the function of antigen-presenting cells by reverse signaling through CD80 and CD86. Abatacept has been shown in clinical trials to reduce disease activity, slow radiographic progression of damage, and improve functional disability. Many patients receive abatacept in combination with methotrexate or another DMARD such as leflunomide. Abatacept therapy has been associated with an increased risk of infection.

Rituximab Rituximab is a chimeric monoclonal antibody directed against CD20, a cell-surface molecule expressed by most mature B lymphocytes. It works by depleting B cells, which in turn, leads to a reduction in the inflammatory response by unknown mechanisms. These mechanisms may include a reduction in autoantibodies, inhibition of T cell activation, and alteration of cytokine production. Rituximab has been approved for the treatment of refractory RA in combination with methotrexate and has been shown to be more effective for patients with seropositive than seronegative disease. Rituximab therapy has been associated with mild to moderate infusion reactions as well as an increased risk of infection. Notably, there have been isolated reports of a potentially lethal brain disorder, progressive multifocal leukoencephalopathy (PML), in association with rituximab therapy, although the absolute risk of this complication appears to be very low in patients with RA. Most of these cases have occurred on a background of previous or current exposure to other potent immunosuppressive drugs.

Tocilizumab Tocilizumab is a humanized monoclonal antibody directed against the membrane and soluble forms of the IL-6 receptor. IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA, with detrimental effects on both joint inflammation and damage. IL-6 binding to its receptor activates intracellular signaling pathways that affect the acute-phase response, cytokine production, and osteoclast activation. Clinical trials attest to the clinical efficacy of tocilizumab therapy for RA, both as monotherapy and in combination with methotrexate and other DMARDs. Tocilizumab has been associated with an increased risk of infection, neutropenia, and thrombocytopenia; however, the hematologic abnormalities appear to be reversible upon stopping the drug. In addition, this agent has been shown to increase LDL cholesterol; however, it is not known as yet if this effect on lipid levels increases the risk for development of atherosclerotic disease.

SMALL-MOLECULE INHIBITORS Because some patients do not adequately respond to conventional DMARDS or biologic therapy, other therapeutic targets have been investigated to fill this gap. Recently, drug development in RA has focused attention on the intracellular signaling pathways that transduce the positive signals of cytokines and other inflammatory mediators that create the positive feedback loops in the immune response. T ese synthetic DMARDs aim to provide the same efficacy as biological therapies in an oral formulation.

Tofacitinib Tofacitinib is a small-molecule inhibitor that primarily inhibits JAK1 and JAK3, which mediate signaling of the receptors for the common γ-chain-related cytokines IL-2, -4, -7, -9, -15, and -21 as well as IFN-γ and IL-6. T ese cytokines all play roles in promoting T and B cell activation as well as inflammation. Tofacitinib, an oral agent, has been shown in randomized, placebo-controlled clinical trials to improve the signs and symptoms of RA significantly over placebo. Major adverse events include elevated serum transaminases indicative of liver injury, neutropenia, increased cholesterol levels, and elevation in serum creatinine. Its use is also associated with an increased risk of infections. Tofacitinib can be used as monotherapy or in combination with methotrexate.

APPROACH TO THE PATIENT: Rheumatoid Arthritis

The original treatment pyramid for RA is now considered to be obsolete and has evolved into a new strategy that focuses on several goals: (1) early, aggressive therapy to prevent joint damage and disability; (2) frequent modification of therapy with utilization of combination therapy where appropriate; (3) individualization of therapy in an attempt to maximize response and minimize side effects; and (4) achieving, whenever possible, remission of clinical disease activity. A considerable amount of evidence supports this intensive treatment approach.

As mentioned earlier, methotrexate is the DMARD of first choice for initial treatment of moderate to severe RA. Failure to achieve adequate improvement with methotrexate therapy calls for a change in DMARD therapy, usually transition to an effective combination regimen. Effective combinations include: methotrexate, sulfasalazine, and hydroxychloroquine (oral triple therapy); methotrexate and leflunomide; and methotrexate plus a biological. The combination of methotrexate and an anti-TNF agent, for example, has been shown in randomized, controlled trials to be superior to methotrexate alone not only for reducing signs and symptoms of disease, but also for retarding the progression of structural joint damage. Predicting which patients will ultimately show radiologic joint damage is imprecise at best, although some factors such as an elevated serum level of acute-phase reactants, high burden of joint inflammation, and the presence of erosive disease are associated with increased likelihood of developing structural injury.

In 2015 a task force of the ACR updated the treatment guidelines for RA. They do make a distinction between patients with early RA (<6 months of disease duration) and patients with established RA. These guidelines highlight the use of a treat-to-target approach and the need to switch or add disease-modifying therapies for worsening or persistent moderate/ high disease activity. In patients with early RA who have persistent moderate/high disease activity on DMARD mono therapy, escalation to combination DMARD therapy or switching to an anti-TNF +/- methotrexate or a non-TNF biologic +/- methotrexate should be considered. It has not been clearly established that a more intensive initial approach is superior to starting with methotrexate alone and, in the absence of an inadequate therapeutic response, moving rapidly to combination DMARD therapy or a anti-TNF or non-TNF biologic agent.

Some patients may not respond to an anti-TNF drug or may be intolerant of its side effects. Initial responders to an anti-TNF agent that later worsen may benefit from switching to another anti-TNF agent. The 2015 guidelines recommend that with loss or lack of effectiveness of anti-TNF, one should switch to another anti-TNF or non-TNF biologic agent. In patients with high disease activity and a serious adverse event from an anti-TNF agent, a non-TNF drug should be used.

Studies have also shown that oral triple therapy (hydroxychloroquine, methotrexate, and sulfasalazine) is a reasonable step for the treatment of early RA, including its use as a step-up strategy where treatment is initiated with methotrexate alone and then combined with hydroxychloroquine and sulfasalazine if the disease is not adequately controlled.

A clinical state defined as low disease activity or remission is the optimal goal of therapy, although most patients never achieve remission despite every effort to achieve it. Composite indices, such as the Disease Activity Score-28 (DAS-28), are useful for classifying states of low disease activity and remission; however, they are imperfect tools due to the limitations of the clinical joint examination in which low-grade synovitis may escape detection. Complete remission has been stringently defined as the total absence of all articular and extraarticular inflammation and immunologic activity related to RA. However, evidence for this state can be difficult to demonstrate in clinical practice. In an effort to standardize and simplify the definition of remission for clinical trials, the ACR and EULAR developed two provisional operational definitions of remission in RA **(Table 6-3)**. A patient may be considered in remission if he or she (1) meets all of the clinical and laboratory criteria listed in Table 6-3 or (2) has a composite SDAI score of <3.3. The SDAI is calculated by taking the sum of a tender joint and swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and CRP (in mg/dL). This definition of remission does not take into account the possibility of subclinical synovitis or that damage alone may produce a tender or swollen joint. Ignoring the semantics of these definitions, the aforementioned remission criteria are nonetheless useful for setting a level of disease control that will likely result in minimal or no progression of structural damage and disability.

PHYSICAL THERAPY AND ASSISTIVE DEVICES All patients should receive a prescription for exercise and physical activity. Dynamic strength training, community-based

TABLE 6-3

ACR/EULAR PROVISIONAL DEFINITION OF REMISSION IN RHEUMATOID ARTHRITIS
At any time point, patient must satisfy all of the following:
Tender joint count ≤1
Swollen joint count ≤1
C-reactive protein ≤1 mg/dL
Patient global assessment ≤1 (on a 0–10 scale)
OR
At any time point, patient must have a Simplified Disease Activity Index score of ≤3.3

Source: Adapted from DT Felson et al: Arthritis Rheum 63:573, 2011.

comprehensive physical therapy, and physical-activity coaching (emphasizing 30 min of moderately intensive activity most days a week) have all been shown to improve muscle strength and perceived health status. Foot orthotics for painful valgus deformity decrease foot pain and resulting disability and functional limitations. Judicious use of wrist splints can also decrease pain; however, their benefits may be offset by decreased dexterity and a variable effect on grip strength.

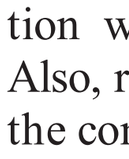
SURGERY Surgical procedures may improve pain and disability in RA—most notably the hands, wrists, and feet, typically after the failure of medical therapy with varying degrees of reported long-term success. For large joints, such as the knee, hip, shoulder, or elbow, total joint arthroplasty is an option for advanced joint disease. A few surgical options exist for dealing with the smaller hand joints. Silicone implants are the most common prosthetic for MCP arthroplasty and are generally implanted in patients with severe decreased arc of motion, marked flexion contractures, MCP joint pain with radiographic abnormalities, and severe ulnar drift. Arthrodesis and total wrist arthroplasty are reserved for patients with severe disease who have substantial pain and functional impairment. T ese two procedures appear to have equal efficacy in terms of pain control and patient satisfaction. Numerous surgical options exist for correction of hallux valgus in the forefoot, including arthrodesis and arthroplasty, as well as primarily arthrodesis for refractory hindfoot pain.

OTHER MANAGEMENT CONSIDERATIONS

Pregnancy Up to 75% of female RA patients will note overall improvement in symptoms during pregnancy, but often will flare after delivery. Flares during pregnancy are generally treated with low doses of prednisone; hydroxychloroquine and sulfasalazine are probably the safest DMARDs to use during pregnancy. Methotrexate and leflunomide therapy are contraindicated during pregnancy due to their teratogenicity in animals and humans. T e experience with biologic agents has been insufficient to make specific recommendations for their use during pregnancy. Most rheumatologists avoid their use in this setting; however, exceptions are considered depending on the circumstances.

Elderly Patients RA presents in up to one-third of patients after the age of 60; however, older individuals may receive less aggressive treatment due to concerns about increased risks of drug toxicity. Studies suggest that conventional DMARDs and biologic agents are equally effective and safe in younger and older patients. Due to comorbidities, many elderly patients have an increased risk of infection. Aging also leads to a gradual decline in renal function that may raise the risk for side effects from NSAIDs and some DMARDS, such as methotrexate. Renal function must be taken into consideration before prescribing methotrexate, which is mostly cleared by the kidneys. To reduce the risks of side effects, methotrexate doses may need to be adjusted downward for the drop in renal function that usually comes with the seventh and eighth decades of life. Methotrexate is usually not prescribed for patients with a serum creatinine greater than 2 mg/dL.

GLOBAL CHALLENGES



Developing countries are finding an increase in the incidence of noncommunicable, chronic diseases such as diabetes, cardiovascular disease, and RA in the face of ongoing poverty, rampant infectious disease, and poor access to modern health care facilities. In these areas, patients tend to have a greater delay in diagnosis and limited access to specialists, and thus greater disease activity and disability at presentation. In addition, infection risk remains a significant issue for the treatment of RA in developing countries because of the immunosuppression associated with the use of glucocorticoids and most DMARDs. For example, in some developing countries, patients undergoing treatment for RA have a substantial increase in the incidence of tuberculosis, which demands the implementation of far more comprehensive screening practices and liberal use of isoniazid prophylaxis than in developed countries. T e increased prevalence of hepatitis B and C, as well as human immunodeficiency virus (HIV), in these developing countries also poses challenges. Reactivation of viral hepatitis has been observed in association with some of the DMARDs, such as rituximab. Also, reduced access to antiretroviral therapy may limit the control of HIV infection and therefore the choice of DMARD therapies.

Despite these challenges, one should attempt to initiate early treatment of RA in the developing countries with the resources at hand. Sulfasalazine and methotrexate are all reasonably accessible throughout the world where they can be used as both monotherapy and in combination with other drugs. T e use of biologic agents is increasing in the developed countries as well as in other areas around the world, although their use is limited by high cost; national protocols restrict their use, and concerns remain about the risk for opportunistic infections.

SUMMARY

Improved understanding of the pathogenesis of RA and its treatment has dramatically revolutionized the management of this disease. T e outcomes of patients with RA are vastly superior to those of the prebiologic modifier era; more patients than in years past are able to avoid significant disability and continue working,

albeit with some job modifications in many cases. The need for early and aggressive treatment of RA as well as frequent follow-up visits for monitoring of drug therapy has implications for our health care system. Primary care physicians and rheumatologists must be prepared to work together as a team to reach the ambitious goals of best practice. In many settings, rheumatologists have reengineered their practice in a way that places high priority on consultations for any new patient with early inflammatory arthritis.

The therapeutic regimens for RA are becoming increasingly complex with the rapidly expanding therapeutic armamentarium. Patients receiving these therapies must be carefully monitored by both the primary care physician and the rheumatologist to minimize the risk of side effects and identify quickly any complications of chronic immunosuppression. Also, prevention and treatment of RA-associated conditions such as ischemic heart disease and osteoporosis will likely benefit from a team approach owing to the value of multidisciplinary care.

Research will continue to search for new therapies with superior efficacy and safety profiles and investigate treatment strategies that can bring the disease under control more rapidly and nearer to remission. However, prevention and cure of RA will likely require new breakthroughs in our understanding of disease pathogenesis. These insights may come from genetic studies illuminating critical pathways in the mechanisms of joint inflammation. Equally ambitious is the lofty goal of biomarker discovery that will open the door to personalized medicine for the care of patients with RA.

CHAPTER 7

ACUTE RHEUMATIC FEVER

Jonathan R. Carapetis

Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A streptococcus. Although many parts of the body may be affected, almost all of the manifestations resolve completely. T e major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared.

GLOBAL CONSIDERATIONS



ARF and RHD are diseases of poverty. T ey were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations. T is decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. T e introduction of antibiotics and improved systems of medical care had a supplemental effect.

T e virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the twentieth century unfortunately was not replicated in developing countries, where these diseases continue unabated. RHD is the most common cause of heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well. It has been estimated that between 15 and 19 million people worldwide are affected by RHD, with approximately one-quarter of a million deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high rates in sub-Saharan Africa, Pacific nations, Australasia, and South and Central Asia. T e pathogenetic pathway from exposure to group A streptococcus followed by pharyngeal infection and subsequent development of ARF, ARF recurrences, and development of RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point **(Fig. 7-1)**. In affluent countries, many of these risk factors are well controlled, and where needed, interventions are in place. Unfortunately, the greatest burden of disease is found in developing countries, most of which do not have the resources, capacity, and/or interest to tackle this multifaceted disease. In particular, almost none of the developing countries has a coordinated, register-based RHD control program, which is proven to be cost effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in developing countries are issues requiring international attention.

EPIDEMIOLOGY

ARF is mainly a disease of children age 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons age >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. T is pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years. T ere is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

PATHOGENESIS

ORGANISM FACTORS

Based on currently available evidence, ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci. Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, in high-incidence regions, it is now thought that any strain of

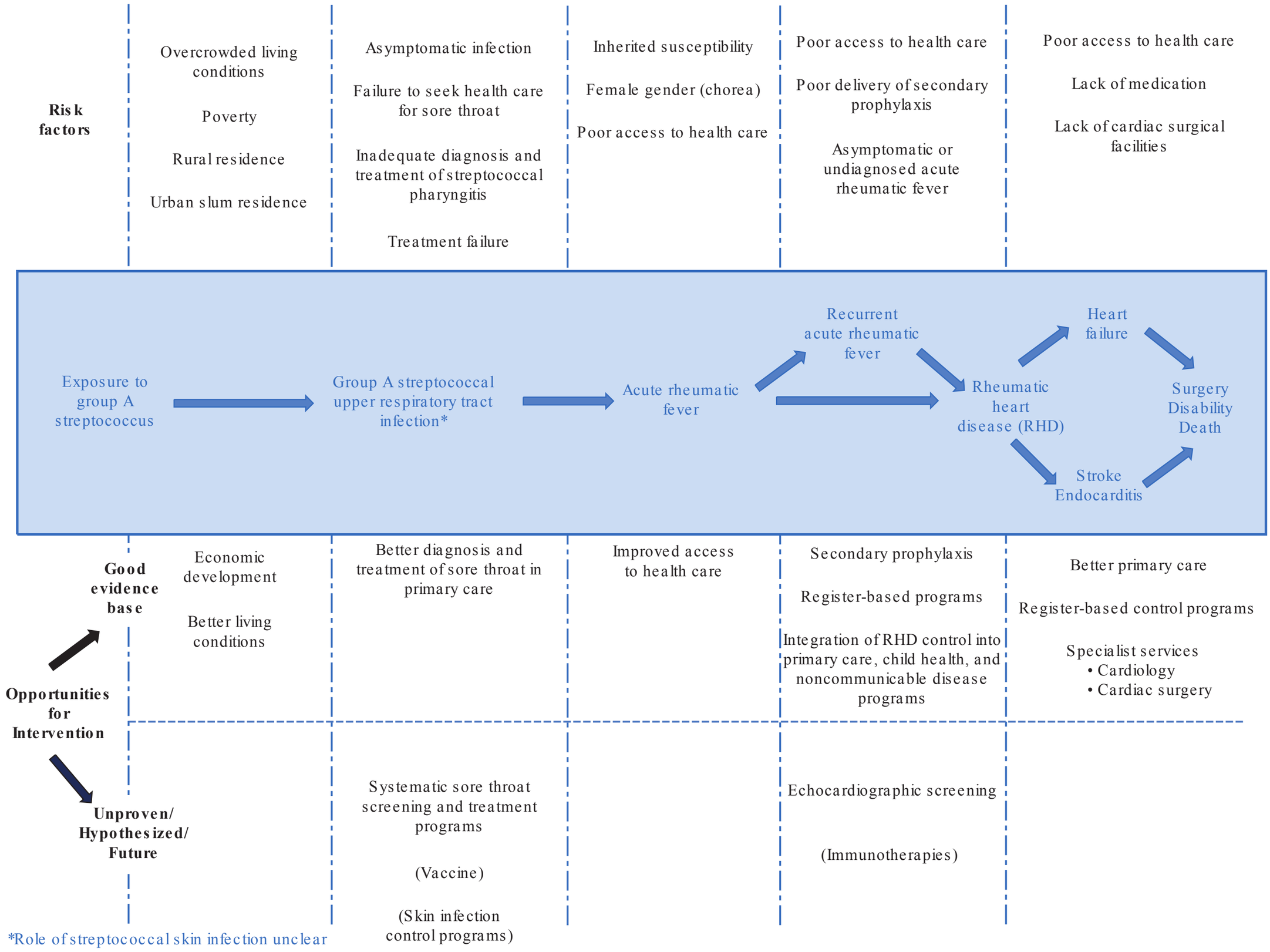


FIGURE 7-1
Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease, with associated risk factors and opportunities for intervention at each step. Interventions in parentheses are either unproven or currently unavailable.

group A streptococcus has the potential to cause ARF. The potential role of skin infection and of groups C and G streptococci is currently being investigated.

HOST FACTORS

Approximately 3–6% of any population may be susceptible to ARF, and this proportion does not vary dramatically between populations. Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic, with 44% concordance in monozygotic twins compared to 12% in dizygotic twins, and heritability more recently estimated at 60%. Most evidence for host factors focuses on immunologic determinants. Some human leukocyte antigen (HLA) class II alleles, particularly HLA-DR7 and HLA-DR4, appear to be associated with susceptibility, whereas other class II alleles have been associated with protection (HLA-DR5, HLA-DR6, HLA-DR51, HLA-DR52, and HLA-DQ). Associations have also been described with polymorphisms at the tumor necrosis factor α locus (TNF-α-308 and TNF-α-238), high levels of circulating mannose-binding lectin, and Toll-like receptors.

THE IMMUNE RESPONSE

The most widely accepted theory of rheumatic fever pathogenesis is based on the concept of molecular mimicry, whereby an immune response targeted at streptococcal antigens (mainly thought to be on the M protein and the N-acetylglucosamine of group A streptococcal carbohydrate) also recognizes human tissues. In this model, cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule VCAM-1, with resulting recruitment of activated lymphocytes and lysis of endothelial

cells in the presence of complement. T e latter leads to release of peptides including laminin, keratin, and tropomyosin, which, in turn, activates cross-reactive T cells that invade the heart, amplifying the damage and causing epitope spreading. An alternative hypothesis proposes that the initial damage is due to streptococcal invasion of epithelial surfaces, with binding of M protein to type IV collagen RHD allowing it to become immunogenic, but not through the mechanism of molecular mimicry.

CLINICAL FEATURES

T ere is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. T e exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. T e most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–60%). T e prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

HEART INVOLVEMENT

Up to 60% of patients with ARF progress to RHD. T e endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. T e mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease. Early valvular damage leads to regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop **(Fig. 7-2)**. **See Videos 7-1 and 7-2 via this web link: https://www.mhprofessional.com/mediacenter/**. T erefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree atrioventricular block or rarely higher level block) and softening of the first heart sound.

People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure. Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it. T ese cases can be diagnosed using echocardiography; auscultation is poorly sensitive and specific for RHD diagnosis in asymptomatic patients. Echocardiographic screening of school-aged children in populations with high rates of RHD is becoming more widespread and has been facilitated by improving technologies in portable echocardiography and the availability of consensus guidelines for the diagnosis of RHD on echocardiography **(Table 7-1)**. Although a diagnosis of definite RHD on screening echocardiography should lead to commencement of secondary prophylaxis, the clinical significance of borderline RHD has yet to be determined.

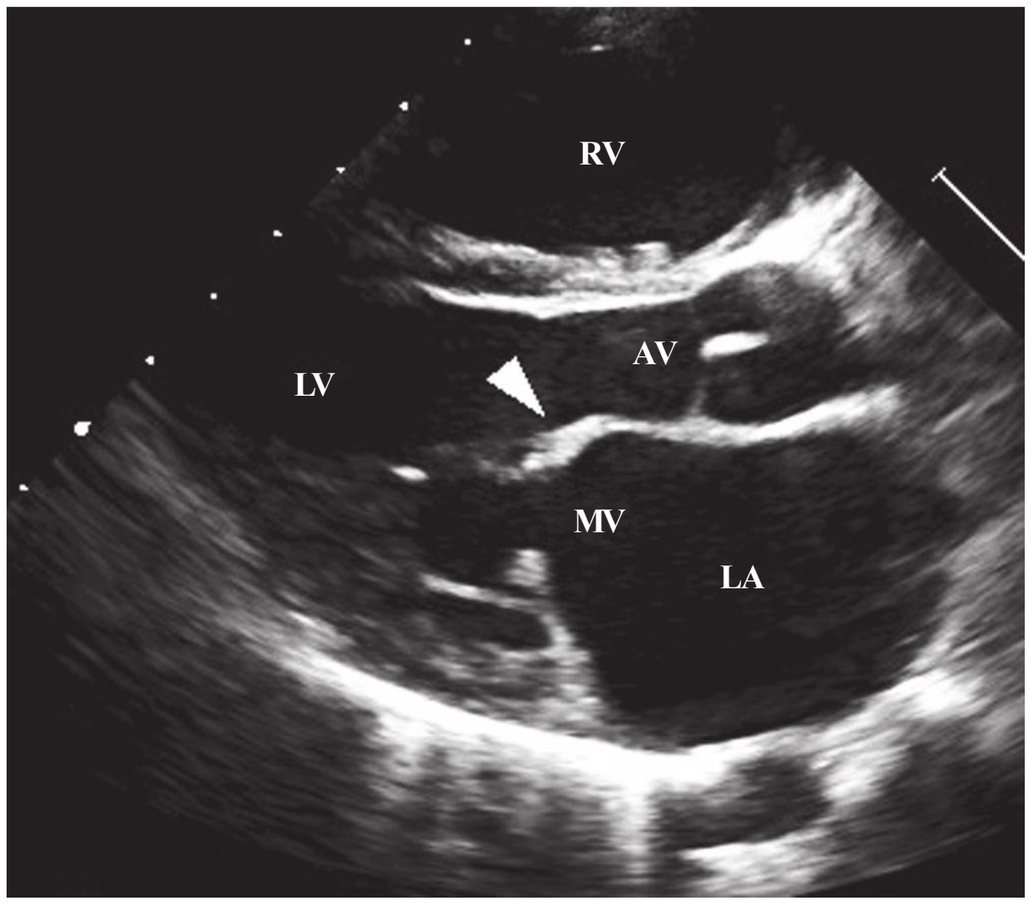


FIGURE 7-2
Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a "hockey stick" or an "elbow" deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (Courtesy of Dr. Bo Remenyi, Department of Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand.)

JOINT INVOLVEMENT

T e most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., polyarthritis). Polyarthritis is typically migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips,

TABLE 7-1

WORLD HEART FEDERATION CRITERIA FOR ECHOCARDIOGRAPHIC DIAGNOSIS OF RHEUMATIC HEART DISEASE (RHD) IN INDIVIDUALS <20 YEARS OF AGE[a]

Definite RHD (either A, B, C, or D):
(A) Pathologic MR and at least two morphologic features of RHD of the mitral valve
(B) MS mean gradient ≥4 mmHg (note: congenital MV anomalies must be excluded)
(C) Pathologic AR and at least two morphologic features of RHD of the AV (note: bicuspid AV and dilated aortic root must be excluded)
(D) Borderline disease of both the MV and AV
Borderline RHD (either A, B, or C):
(A) At least two morphologic features of RHD of the MV without pathologic MR or MS
(B) Pathologic MR
(C) Pathologic AR
Normal Echocardiographic Findings (all of A, B, C, and D):
(A) MR that does not meet all four Doppler criteria (physiologic MR)
(B) AR that does not meet all four Doppler criteria (physiologic AR)
(C) An isolated morphologic feature of RHD of the MV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
(D) Morphologic feature of RHD of the AV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
Definitions of Pathologic Regurgitation and Morphologic Features of RHD:
Pathologic MR: All of the following: seen in two views; in at least one view, jet length 2 cm; peak velocity ≥3 m/s; pansystolic jet in at least one envelope
Pathologic AR: All of the following: seen in two views; in at least one view, jet length ≥1 cm; peak velocity ≥3 m/s; pandiastolic jet in at least one envelope
Morphologic features of RHD in MV: anterior MV leaflet thickening ≥3 mm (age specific); chordal thickening; restricted leaflet motion; excessive leaflet tip motion during systole
Morphologic features of RHD in AV: irregular or focal thickening; coaptation defect; restricted leaflet motion; prolapse

[a]For criteria in individuals >20 years of age, see source document.
Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.
Source: Adapted from Remenyi B et al: World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. Nat Rev Cardiol 9:297–309, 2012.

and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

CHOREA

Sydenham's chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs. They may be generalized or restricted to one side of the body (hemi-chorea). In mild cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living. There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the choreiform movements (which usually resolve within 6 weeks but sometimes may take up to 6 months).

SKIN MANIFESTATIONS

The classic rash of ARF is erythema marginatum, which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

OTHER FEATURES

Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever (≥39°C) is the rule, lower grade temperature elevations are not uncommon. Elevated acute-phase reactants are also present in most cases.

EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis of ARF. Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most common serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

CONFIRMING THE DIAGNOSIS

Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the Jones criteria) to aid in the diagnosis. The most recent revision of the Jones criteria **(Table 7-2)** require the clinician to determine if the patient is from a setting or population known to experience low rates of ARF. For this group, there is a set of "low-risk" criteria; for all others, there is a set of more sensitive criteria.

TABLE 7-2

REVISED JONES CRITERIA, 2015

DIAGNOSTIC CATEGORIES	CRITERIA
A. For all patient populations with evidence of preceding group A streptococcal infection	
Diagnosis: initial ARF	2 Major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 Major or 1 major and 2 minor or 3 minor
B. Major criteria	
Low-risk populations[a] Carditis[b] • Clinical and/or subclinical Arthritis • Polyarthritis only Chorea Erythema marginatum SC nodules	Moderate- and high-risk populations Carditis • Clinical and/or subclinical Arthritis • Monoarthritis or polyarthritis • Polyarthralgia[c] Chorea Erythema marginatum SC nodules
C. Minor criteria	
Low-risk populations[a] Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL[d] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Moderate- and high-risk populations Monoarthralgia Fever (≥38°C) ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL[d] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

[a]Low-risk populations are those with ARF incidence ≤2 per 100,000 school-age children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year.

[b]Subclinical carditis indicates echocardiographic valvulitis. (See source document.)

[c]Polyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. (See source document for more information.)

[d]CRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Source: Gewitz MH et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. Circulation 131:1806, 2015.

TREATMENT Acute Rheumatic Fever

Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment of heart failure and other symptoms is undertaken, and preventive measures including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis. Other tests that should be performed are listed in **Table 7-3**.

There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of, RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

ANTIBIOTICS All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection. Penicillin is the drug of choice and can be given orally (as phenoxymethyl penicillin, 500 mg [250 mg for children ≤27 kg] PO twice daily, or amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days) or as a single dose of 1.2 million units (600,000 units for children ≤27 kg) IM benzathine penicillin G.

SALICYLATES AND NSAIDs These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed. They are of no proven value in the treatment of carditis or chorea. Aspirin is the drug of choice, delivered at a dose of 50–60 mg/kg per day, up to a maximum of 80–100 mg/kg

per day (4–8 g/d in adults) in four to five divided doses. At higher doses, the patient should be monitored for symptoms of salicylate toxicity such as nausea, vomiting, or tinnitus; if symptoms appear, lower doses should be used. When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses can have the dose reduced to 50–60 mg/kg per day for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. T is does not indicate a recurrence and can be managed by recommencing salicylates for a brief period. Naproxen at a dose of 10–20 mg/kg per day is a suitable alternative to aspirin and has the advantage of twice-daily dosing.

CONGESTIVE HEART FAILURE

Glucocorticoids The use of glucocorticoids in ARF remains controversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer term outcome of carditis. However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects. If used, prednisone or prednisolone is recommended at a dose of 1–2 mg/kg per day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks.

BED REST Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.

CHOREA Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be managed by providing a calm environment. In patients with severe chorea, carbamazepine or sodium valproate is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside. T ere is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea. T ey should be considered in severe or refractory cases. Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) Small studies have suggested that IVIg may lead to more rapid resolution of chorea but have shown no benefit on the short- or long-term outcome of carditis in ARF without chorea. In the absence of better data, IVIg is not recommended except in cases of severe chorea refractory to other treatments.

TABLE 7-3

RECOMMENDED TESTS IN CASES OF POSSIBLE ACUTE RHEUMATIC FEVER

Recommended for All Cases
White blood cell count
Erythrocyte sedimentation rate
C-reactive protein
Blood cultures if febrile
Electrocardiogram (if prolonged P-R interval or other rhythm abnormality, repeat in 2 weeks and again at 2 months if still abnormal)
Chest x-ray if clinical or echocardiographic evidence of carditis
Echocardiogram (consider repeating after 1 month if negative)
Throat swab (preferably before giving antibiotics)—culture for group A streptococcus
Antistreptococcal serology: both anti-streptolysin O and anti-DNase B titers, if available (repeat 10–14 days later if first test not confirmatory)
Tests for Alternative Diagnoses, Depending on Clinical Features
Repeated blood cultures if possible endocarditis
Joint aspirate (microscopy and culture) for possible septic arthritis
Copper, ceruloplasmin, antinuclear antibody, drug screen for choreiform movements
Serology and autoimmune markers for arboviral, autoimmune, or reactive arthritis

Source: Reprinted with permission from Menzies School of Health Research.

PROGNOSIS

Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.

Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary prophylaxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis.

PREVENTION

PRIMARY PREVENTION

Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. T is is dif cult to achieve in most places where ARF is common.

T erefore, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed. In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries, primary care guidelines often recommend that all patients with sore throat be treated with penicillin or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis. Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A streptococcus.

SECONDARY PREVENTION

T e mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. T e best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with an every-4-week dosing schedule can be achieved, more frequent dosing is rarely needed. Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.

T e duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence because of the potentially serious consequences) **(Table 7-4)**. Secondary prophylaxis is best delivered as part of a coordinated RHD control program, based around a registry of patients. Registries improve the ability to follow patients and identify those who default from prophylaxis and to institute strategies to improve adherence.

TABLE 7-4

AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR DURATION OF SECONDARY PROPHYLAXIS[a]

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

[a]These are only recommendations and must be modif ed by individual circumstances as warranted. Note that some organizations recommend a minimum of 10 years of prophylaxis after the most recent episode, or until 21 years of age (whichever is longer), regardless of the presence of carditis with the initial episode.

Source: Adapted from AHA Scientif c Statement Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis. Circulation 119:1541, 2009.

Videos can be accessed via the following link: https://www.mhprofessional.com/mediacenter/.

VIDEO 7-1A Transthoracic echocardiographic images of a 9-year-old girl with f rst episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. T e valve leaflets are relatively thin and highly mobile. T e failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. T e mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. A. Acute rheumatic carditis (apical four-chamber view echocardiogram).

VIDEO 7-1B Transthoracic echocardiographic images of a 9-year-old girl with f rst episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. T e valve leaflets are relatively thin and highly mobile. T e failure of coaptation of the mitral valve leaflets is the result of chordal

elongation and annular dilatation. T e mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. B. Acute rheumatic carditis (apical four-chamber view color Doppler echocardiogram).

VIDEO 7-1C Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. T e valve leaflets are relatively thin and highly mobile. T e failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. T e mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. C. Acute rheumatic carditis (parasternal long-axis view echocardiogram).

VIDEO 7-1D Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever.

Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. T e valve leaflets are relatively thin and highly mobile. T e failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. T e mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. D. Acute rheumatic carditis (parasternal long-axis view color Doppler echocardiogram).

VIDEO 7-2A Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis.

Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. T is appearance is commonly described as a “hockey stick” or an “elbow” deformity. A. Chronic rheumatic heart disease (parasternal long-axis view).

VIDEO 7-2B Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis.

Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. T is appearance is commonly described as a “hockey stick” or an “elbow” deformity. B. Chronic rheumatic heart disease (apical two-chamber view echocardiogram).

CHAPTER 8

SYSTEMIC SCLEROSIS (SCLERODERMA) AND RELATED DISORDERS

John Varga

DEFINITION

Systemic sclerosis (SSc) is an uncommon connective tissue disorder characterized by multisystem involvement, heterogeneous clinical manifestations, a chronic and often progressive course, and significant disability and mortality. Multiple genes contribute to disease susceptibility; however, environmental exposures are likely to play a major role in causing SSc. T e early stage of the disease is associated with prominent inflammatory features. Over time, functional and structural alterations in multiple vascular beds and progressive visceral organ dysfunction due to fibrosis dominate the clinical picture. Although thickened skin (scleroderma) is the distinguishing hallmark of SSc, skin induration can occur in localized forms of scleroderma and other disorders **(Table 8-1)**. Patients with SSc can be broadly grouped into diffuse cutaneous and limited cutaneous subsets defined by the pattern of skin involvement, as well as clinical and laboratory features **(Table 8-2)**. Diffuse cutaneous SSc (dcSSc) is associated with extensive skin induration, starting in the fingers and ascending from distal to proximal limbs and the trunk. T ese patients often have early interstitial lung disease and acute renal involvement. In contrast, in patients with limited cutaneous SSc (lcSSc), Raynaud's phenomenon may precede other manifestations of SSc by years. In these patients, skin involvement remains limited to the fingers (sclerodactyly), distal limbs, and face, and the trunk is not affected. T e constellation of calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, seen in some lcSSc patients, is termed the CREST syndrome. Visceral organ involvement in lcSSc tends to show insidious progression, and pulmonary arterial hypertension (PAH), interstitial lung disease, hypothyroidism, and primary biliary cirrhosis may occur as late complications. In some patients, Raynaud's phenomenon and other characteristic features of SSc occur in the absence of skin thickening. T is syndrome has been termed SSc sine scleroderma.

TABLE 8-1

CONDITIONS ASSOCIATED WITH SKIN INDURATION

- Systemic sclerosis (SSc)
  - Limited cutaneous SSc
  - Diffuse cutaneous SSc
- Localized scleroderma
  - Guttate (plaque) morphea, diffuse (pansclerotic) morphea, bullous morphea
  - Linear scleroderma, coup de sabre, hemifacial atrophy
- Pansclerotic morphea
- Overlap syndromes
  - Mixed connective tissue disease
  - SSc/polymyositis
- Stiff skin syndrome
- Diabetic scleredema and scleredema of Buschke
- Scleromyxedema (papular mucinosis)
- Chronic graft-versus-host disease
- Diffuse fasciitis with eosinophilia (Shulman's disease, eosinophilic fasciitis)
- Chemically induced and drug-associated scleroderma-like conditions
  - Vinyl chloride–induced disease
  - Eosinophilia-myalgia syndrome (associated with l-tryptophan)
  - Nephrogenic systemic fibrosis (associated with gadolinium)
- Paraneoplastic syndrome

EPIDEMIOLOGY

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. In the United States, the incidence is estimated at 9–19 cases per million per year.

TABLE 8-2

SUBSETS OF SYSTEMIC SCLEROSIS (SSC): FEATURES OF LIMITED CUTANEOUS SSC VERSUS DIFFUSE CUTANEOUS SSC

CHARACTERISTIC FEATURE	LIMITED CUTANEOUS SSC	DIFFUSE CUTANEOUS SSC
Skin involvement	Indolent onset. Limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Antedates skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequent, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; generally early (<4 years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anticentromere	Anti–topoisomerase I (Scl-70), anti-RNA polymerase III

T e only community-based survey of SSc yielded a prevalence of 286 cases per million. T ere are an estimated 100,000 cases in the United States, although this number may be significantly higher if patients who do not meet strict classification criteria are also included. Rates of SSc in England, Australia, and Japan appear to be lower. Age, gender, and ethnicity are important in disease susceptibility. In common with other connective tissue diseases, SSc shows a strong female predominance (4.6:1), which is most pronounced in the childbearing years and declines after menopause. Although SSc can present at any age, the peak age of onset for both limited and diffuse cutaneous forms is 30–50 years. T e incidence is higher in blacks than whites, and disease onset occurs at an earlier age. Furthermore, blacks with SSc are more likely to have diffuse cutaneous disease associated with interstitial lung involvement and a worse prognosis.

GENETIC CONSIDERATIONS



In general, SSc shows modest heritability, and the genetic associations identified to date make only a small contribution to disease susceptibility. Concordance rates for SSc are low (4.7%) in monozygotic twins, although concordance for antinuclear antibody (ANA) positivity is significantly higher. On the other hand, evidence for genetic contribution to disease susceptibility is provided by the observation that 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate markedly increased compared to the general population. T e risk of Raynaud's phenomenon, interstitial lung disease, and other autoimmune diseases, including systemic lupus erythematosus (SLE) **(Chap. 4)**, rheumatoid arthritis **(Chap. 6)**, and autoimmune thyroiditis, is also increased. Approaches to study the role of genetics in SSc use candidate gene single nucleotide polymorphism (SNP) analysis and genome-wide association studies (GWASs). Candidate gene studies in SSc have shown associations with multiple gene variants, many related to B and T lymphocyte activation and signaling (BANK1, BLK, CD247, CSK, IRAK1, IL2RA, PTPN22, and TNIP1). IRAK1, which codes for a gene involved in both innate and adaptive immunity, is the first X-linked gene associated with SSc and may contribute to female predominance. Other gene variants associated with SSc are involved in innate immunity and the interferon pathways (IRF5, IRF7, STAT4, TNFAIP3, and TLR2). In addition, candidate gene studies and GWAS both identified association with genes in the major histocompatibility complex (MHC), including NOTCH4 and PSORSC1. In addition to disease susceptibility, some of these genetic loci are associated with particular SSc disease manifestations or serologic subsets, including interstitial lung disease (ILD) (CTGF, CD226), PAH (TNIP1), and scleroderma renal crisis (HLA-DRB1*). Although the functional consequences of these gene variants are currently not well understood, they may result in altered immune function, leading to increased susceptibility to autoimmunity and inflammation. Of note, many of the genetic variants associated with SSc are also seen in other autoimmune disorders, including SLE, rheumatoid arthritis, and psoriasis, suggesting common pathways shared among these conditions. T e genetic associations identified to date only explain a fraction of the heritability of SSc, and GWASs, fine mapping, and resequencing of DNA regions of interest to identify additional genetic susceptibility factors in SSc, particularly rare variants, are currently ongoing.

ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS

Given the relatively modest genetic contribution to disease susceptibility, environmental factors, such as infectious agents, intestinal microbiota, and occupational, dietary, and drug exposures, are likely to play a major role in causing SSc. Patients with SSc show evidence of chronic infection of lesional tissue with Epstein-Barr virus (EBV). T ey also have increased antibodies to human cytomegalovirus (hCMV), and anti–topoisomerase I (Scl-70) autoantibodies recognize hCMV-associated antigenic epitopes, suggesting molecular mimicry as a possible mechanistic link between hCMV infection and SSc. An epidemic of a novel syndrome with features suggestive of SSc occurred in Spain in the 1980s. T e outbreak, termed toxic oil syndrome, was linked to contaminated rapeseed oils used for cooking. Another epidemic outbreak, termed eosinophilia-myalgia syndrome (EMS), occurred a decade later and was linked to the consumption of l-tryptophan-containing dietary supplements. Although both of these novel toxic-epidemic syndromes were characterized by scleroderma-like chronic skin changes and variable visceral organ involvement, they were associated with clinical, pathologic, and laboratory features distinguishing them from SSc. Occupational exposures tentatively linked with SSc include silica dust in miners, polyvinyl chloride, epoxy resins, and aromatic hydrocarbons including toluene and trichloroethylene. Drugs implicated in SSc-like illnesses include bleomycin, pentazocine, and cocaine, and appetite suppressants linked with pulmonary hypertension. Although case reports and series describing SSc in women with silicone breast implants had raised concern regarding a possible causal role of silicone in SSc, large-scale epidemiologic investigations found no evidence of increased prevalence of SSc.

PATHOGENESIS

T e following three cardinal pathophysiologic processes account for the protean clinical manifestations of SSc: (1) diffuse microangiopathy, (2) inflammation and autoimmunity, and (3) visceral and vascular fibrosis in multiple organs **(Fig. 8-1)**. Autoimmunity and altered vascular reactivity are early manifestations. Complex and dynamic interplay between these processes initiates and then amplifies the fibrotic process.

ANIMAL MODELS OF DISEASE

No single animal model of SSc fully reproduces the three cardinal processes that underlie the pathogenesis, but some recapitulate selected aspects of the human

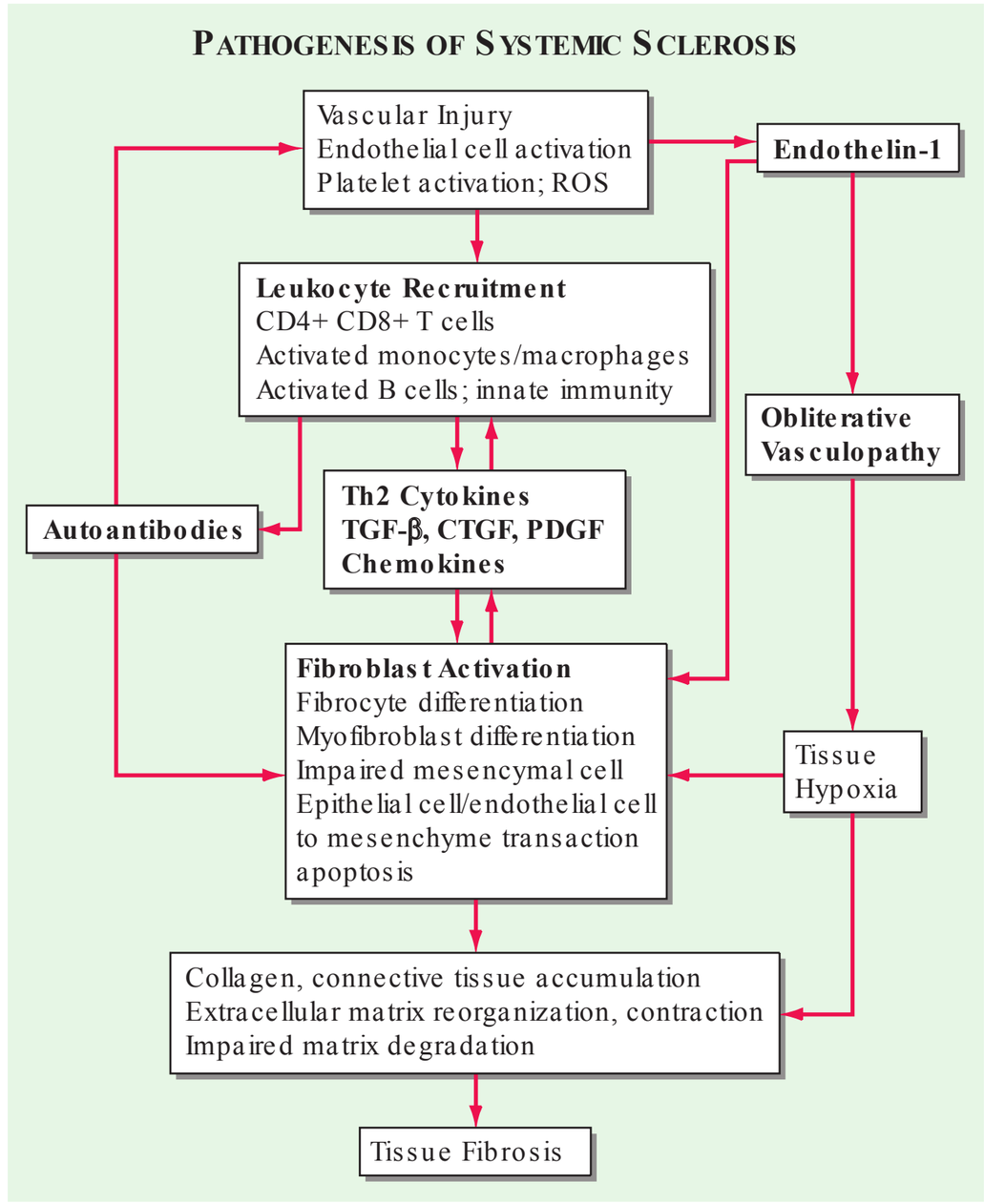


FIGURE 8-1
Initial vascular injury in a genetically susceptible individual leads to **f**unctional and structural vascular alterations, in**fl**ammation, and autoimmunity. The infammatory and immune responses initiate and sustain fibroblast activation and differentiation, resulting in pathologic fibrogenesis and irreversible tissue damage. Vascular damage results in tissue ischemia that further contributes to progressive fibrosis and atrophy. C TGF, connective tissue growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β.

disease, including fibrosis, microvascular involvement, and autoimmunity. Tight-skin mice (Tsk1) develop spontaneous skin thickening due to a mutation in the fibrillin-1 gene. T e mutant fibrillin-1 protein disrupts extracellular matrix assembly and causes aberrant activation of transforming growth factor β (TGF-β). Fibrillin-1 mutations are associated with Marfan's disease as well as the stiff skin syndrome but not SSc. Skin and lung fibrosis can be induced in mice by injection of bleomycin, HOCl, or double-stranded RNA or by transplantation of human leukocyte antigen (HLA)–mismatched bone marrow or spleen cells. Targeted genetic modifications in mice give rise to new disease models for dissecting the pathogenetic roles of individual molecules, cell types, and networks. For example, mice lacking Smad3, an intracellular TGF-β signal transducer, adiponectin, or the nuclear receptor peroxisome proliferator-activated receptor (PPAR) γ or overexpressing Wnt10b or adiponectin were either resistant

or hypersensitive to chemically induced experimental scleroderma. T ese mouse models have potential utility in preclinical evaluation of potential therapies.

MICROANGIOPATHY

Involvement of small blood vessels in SSc affects multiple vascular beds and has important clinical sequelae including Raynaud's phenomenon, ischemic digital ulcers, scleroderma renal crisis, and PAH. Raynaud's phenomenon, an early disease manifestation, is characterized by an altered blood-flow response to cold challenge. T is initially reversible functional abnormality is associated with autonomic and peripheral nervous system alterations, including impaired production of the neuropeptide calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α_2-adrenergic receptors on vascular smooth-muscle cells. Isolated (primary) Raynaud's phenomenon is extremely common and generally benign and nonprogressive. In contrast, SSc-associated Raynaud's phenomenon is often progressive and complicated by irreversible structural changes, culminating in ischemic digital ulcers and loss of digits. Viruses, vascular cytotoxic factors, thrombogenic microparticles, complement and autoantibodies to phospholipids, β2 glycoprotein I (β2GPI), and endothelial cells are suspected triggers of endothelial cell injury in SSc. Endothelial injury results in dysregulated production of endothelium-derivedvasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) substances, as well as increased expression of intercellular adhesion molecule 1 (ICAM-1) and other surface adhesion molecules. Microvessels show enhanced permeability and transendothelial leukocyte diapedesis, abnormal activation of coagulation cascades, elevated thrombin production, and impaired fibrinolysis. Spontaneous platelet aggregation causes release of serotonin, platelet-derived growth factor (PDGF), and platelet alpha granules including thromboxane, a potent vasoconstrictor. Smooth-muscle cell–like myointimal cells proliferate, the basement membrane is thickened and reduplicated, and fibrosis of the adventitial layers develops. T e vasculopathic process affects capillaries, as well as arterioles, and even large vessels in many organs, resulting in reduced blood flow andtissue ischemia. Progressive luminal occlusion due to intimal and medial hypertrophy, combined with persistent endothelial cell damage and adventitial fibrosis, establish a vicious cycle that culminates in the striking absence of blood vessels (rarefaction) in late-stage disease. Recurrent ischemia-reperfusion generates reactive oxygen species (ROS) that further damage the endothelium through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally reestablishes blood flow to ischemic tissue is defective in SSc despite elevated levels of vascular endothelial growth factor (VEGF) and other angiogenic factors. Moreover, the number of bone marrow–derived circulating endothelial progenitor cells is reduced. T us, widespread capillary loss, obliterative vasculopathy of small and medium-sized arteries, and failure to repair damaged vessels are hallmarks of SSc.

IMMUNE DYSREGULATION

Cellular immunity

T e following observations highlight the autoimmune nature of SSc: presence of circulating autoantibodies; familial clustering of SSc with other autoimmune diseases; detection of immune cells, including T cells with oligoclonal antigen receptors, in target organs; elevated circulating levels and spontaneous secretion from blood mononuclear cells of inflammatory cytokines and chemokines such as interleukin (IL) 1, IL-4, IL-10, IL-17, IL-33, CCL2, and CXCL4; and the association with variants in genes functionally implicated in immune responses. Genetic studies in SSc reveal strong and consistent associations with major histocompatibility locus alleles, as well as non-HLA-linked genes encoding mediators of both adaptive and innate immune responses (CD247, STAT4, IRF5, CD226, and TNFSF4). In early SSc, mononuclear inflammatory cell infiltrates comprised of activated T cells, monocytes/macrophages, and dendritic cells can be seen in skin, lungs, and other affected organs prior to appearance of fibrosis or vascular damage. Dendritic cells and T cells can often be found in close proximity to activated fibroblasts and myofibroblasts. Tissue-infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T cell receptor signatures indicative of oligoclonal expansion in response to (unknown) antigen. Circulating T cells have elevated levels of chemokine receptors and α_1 integrin adhesion molecules, accounting for their enhanced binding to endothelium and to fibroblasts. Endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated macrophages and T cells show a T_H2-polarized type 2 immune response driven by dendritic cells and thymic stromal lymphopoietin. T_H2 cytokines such as IL-4 and IL-13 induce fibroblast activation and alternate M2 macrophage polarization, whereas the T_H1 cytokine interferon γ (IFN-γ) blocks cytokine-mediated fibroblast activation. Alternately activated M2 macrophages produce TGF-β and promote fibrosis. Although the frequency of circulating regulatory T cells that enforce immune tolerance is elevated in SSc, their immunosuppressive function is defective. Molecular characterization of SSc skin biopsies using DNA microarrays identifies a subset showing markedly elevated expression of

inflammation-associated genes, particularly chemokines and their receptors, interferon response genes, and mediators of innate immunity. Evidence of activated innate immunity and toll-like receptor signaling, indicative of activation by type 1 interferon produced by plasmacytoid dendritic cells, is prominent in peripheral blood cells.

Humoral autoimmunity

Circulating ANAs can be detected in virtually all patients with SSc. In addition, a number of SSc-specific autoantibodies have been described. T ese SSc-specific antibodies show strong association with distinct disease endophenotypes **(Table 8-3)**. While most are directed against intracellular proteins associated with cell proliferation, such as topoisomerase I and RNA polymerases I, II, and III, others are directed against cell-surface antigens, receptors, or secreted proteins. Autoantibodies have clinical utility as diagnostic and prognostic biomarkers in SSc, and some, such as antibodies directed against the angiotensin II receptor or the PDGF receptor, may have a direct pathogenic role.

A variety of mechanisms have been proposed for the development of autoantibodies in SSc. Proteolytic cleavage, increased expression, or altered subcellular localization of certain cellular proteins in SSc could lead to their recognition as neoepitopes by the immune system, resulting in breakdown of immune tolerance. B cells are implicated in both the autoimmune and fibrotic process in SSc. In addition to antibody production, B cells also present antigen, secrete IL-6 and TGF-β, and modulate T cell and dendritic cell function.

TABLE 8-3

AUTOANTIBODIES AND ASSOCIATED FEATURES IN SYSTEMIC SCLEROSIS (SSC)

TARGET ANTIGEN	SSC SUBSET	CHARACTERISTIC CLINICAL ASSOCIATION
Topoisomerase I	dcSSc	Tendon friction rubs, early ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins	lcSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH, overlap syndromes; renal crisis rare
RNA polymerase III	dcSSc	Rapidly progressive skin involvement, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers
U3-RNP (fibrillarin)	dcSSc	PAH, ILD, scleroderma renal crisis, myositis
Th/T0	lcSSc	ILD, PAH
PM/Scl	lcSSc	Calcinosis cutis, ILD, myositis overlap
Ku	Overlap	SLE, myositis
U1-RNP	MCTD	PAH, arthritis, myositis

Abbreviations: dcSSc, diffuse cutaneous SSc; GAVE, gastric antral vascular ectasia; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MCTD, mixed connective tissuedisease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

FIBROSIS

Fibrosis affecting multiple organs, a distinguishing feature of SSc, is characterized by progressive replacement of normal tissue architecture with dense, stiff, and acellular connective tissue. Fibrosis characteristically follows, and is thought to be a consequence of, inflammation, autoimmunity, and microvascular damage. Fibroblasts are mesenchymal cells responsible for maintaining the functional and structural integrity of connective tissue. Upon activation by TGF-β and other extracellular cues, fibroblasts proliferate; migrate; secrete collagens, growth factors, chemokines, and cytokines; and transdifferentiate into contractile myofibroblasts. Under normal conditions, these fibrotic responses constitute self-limited physiologic remodeling necessary for tissue repair and regeneration. When these responses become sustained and amplified, pathologic fibrosis results. Autocrine stimulatory signaling by endogenously produced TGF-β and fibrotic mediators such as hypoxia, ROS, thrombin, Wnt ligands, connective tissue growth factor (CTGF), PDGF, lysophosphatidic acid, endothelin-1, mechanical forces, and endogenous ligands for toll-like receptors are responsible for maintaining sustained fibroblast activation underlying progressive fibrosis in SSc.

In addition to tissue-resident fibroblasts and transformation of epithelial cells into fibroblasts, bone marrow–derived circulating mesenchymal progenitor cells also contribute to fibrosis. T e factors that regulate the differentiation of mesenchymal progenitor cells and their traf cking from the circulation into lesional tissue are unknown. Epithelial and endothelial cells, mesenchymal progenitor cells, and tissue fibroblasts can differentiate into smooth-muscle-like myofibroblasts. Although myofibroblasts can be detected transiently during normal wound healing, they persist in fibrotic tissue, possibly due to resistance to apoptosis, and contribute to scar formation via production of collagen and TGF-β and contraction of the surrounding extracellular matrix.

Explanted SSc fibroblasts may display an abnormally activated phenotype ex vivo, with variably increased rates of collagen gene transcription, spontaneous ROS generation, and constitutive expression of alpha smooth-muscle actin stress fibers. T e persistence of the "scleroderma phenotype" of these cells during their

serial passage in vitro may reflect autocrine TGF-β stimulatory loops, deregulated microRNA expressions, histone acetylation, and other epigenetic modifications.

PATHOLOGY

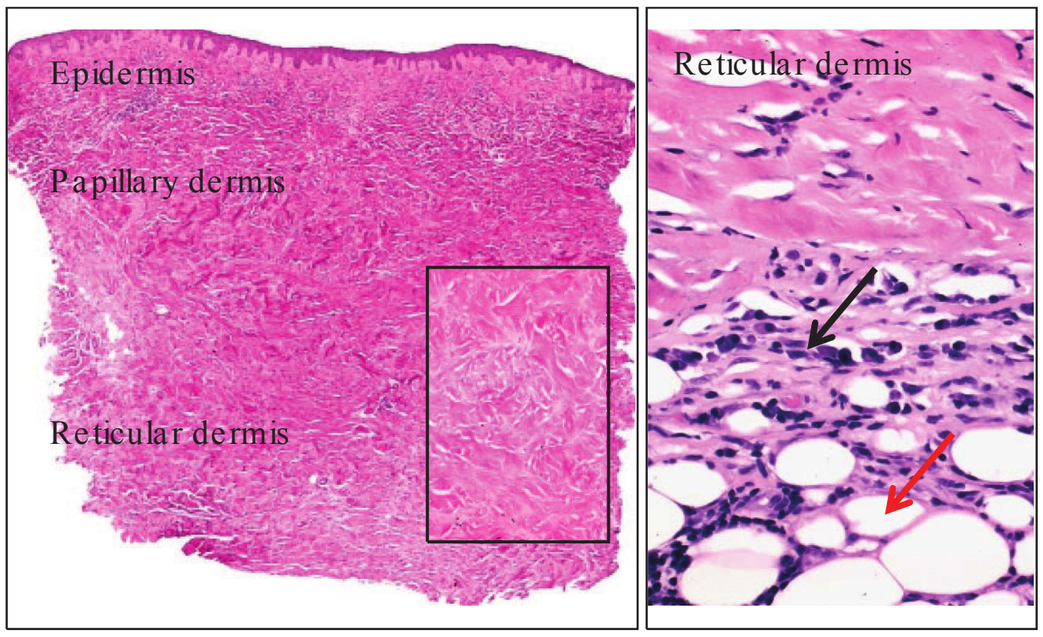
The distinguishing pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative microangiopathy, together with fibrosis in the skin and internal organs. In early disease, perivascular inflammatory cell infiltrates composed of T lymphocytes, monocytes/macrophages, plasma cells, mast cells, and occasionally B cells may be detected in multiple organs. A bland noninflammatory obliterative vasculopathy as a late finding is prominent in the heart, lungs, kidneys, and intestinal tract. Fibrosis is found in the skin, lungs, gastrointestinal tract, heart, tendon sheaths, perifascicular tissue surrounding skeletal muscle, and some endocrine organs. In these tissues, accumulation of collagens, fibronectin, proteoglycans, tenascin, cartilage oligomeric matrix protein (COMP), and other structural macromolecules progressively disrupts normal architecture, resulting in impaired function of affected organs.

SKIN

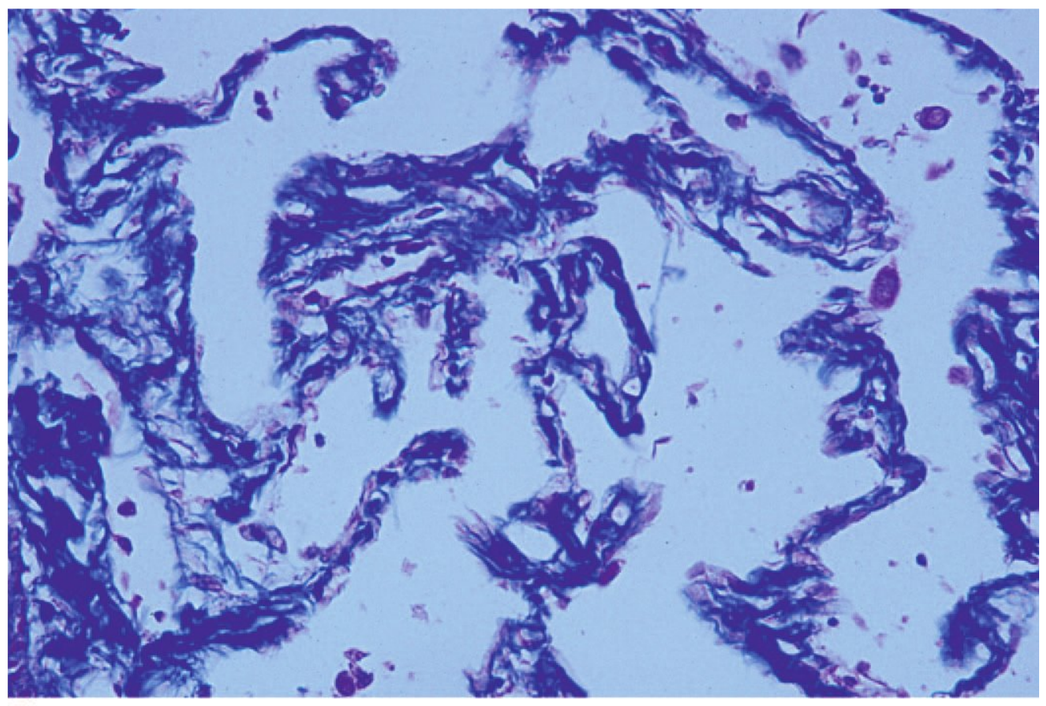
In the skin, fibrosis causes dermal expansion and obliteration of the hair follicles, eccrine glands, and other appendages **(Fig. 8-2A)**. Collagen fiber accumulation is most prominent in the reticular dermis, and the fibrotic process invades the subjacent adipose layer with entrapment of adipocytes. With disease progression, the intradermal adipose layer is diminished and may completely disappear. The epidermis is atrophic, and the rete pegs are effaced.

LUNGS

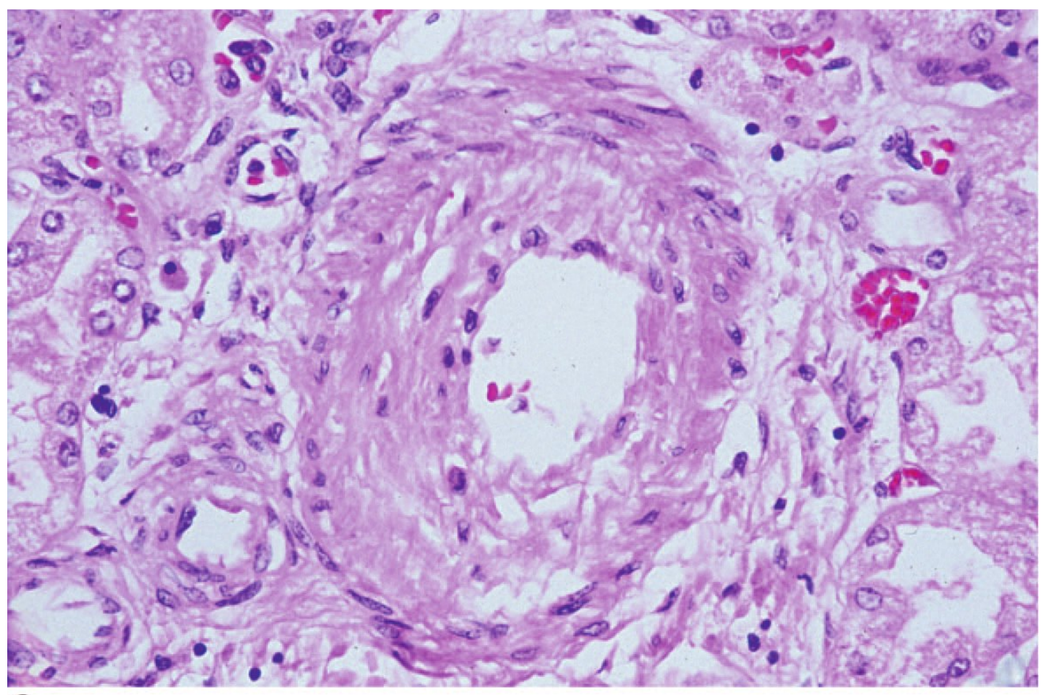
Patchy infiltration of the alveolar walls with T lymphocytes, macrophages, and eosinophils occurs in early disease. With progression, interstitial fibrosis and vascular damage dominate the pathologic picture, often coexisting within the same lesions in patients with dcSSc. Pulmonary fibrosis is characterized by expansion of the alveolar interstitium, with accumulation of collagen and other matrix proteins. The most common histologic pattern in SSc-associated ILD is nonspecific interstitial pneumonia (NSIP), distinct from the usual interstitial pneumonia (UIP) pattern characteristically seen in patients with idiopathic pulmonary fibrosis **(Fig. 8-2B)**. Progressive thickening of the alveolar septae results in obliteration of the airspaces and loss of pulmonary



A



B



C

FIGURE 8-2

Pathologic findings in systemic sclerosis (SSc). A. Left panel: The skin is thickened due the marked expansion of the dermis. Inset, higher magnification showing thick hyalinized collagen bundles replace skin appendages. Right panel: Inflammation in the reticular dermis. Mononuclear inflammatory cells infiltrating the dermis and intradermal adipose tissue. B. Early interstitial lung disease. Diffuse fibrosis of the alveolar septae and a chronic inflammatory cell infiltrate. Trichrome stain. C. Pulmonary arterial obliterative vasculopathy. Striking intimal hyperplasia and narrowing of the lumen of a small pulmonary artery, with minimal interstitial fibrosis, in a patient with limited cutaneous SSc.

blood vessels. T is process impairs gas exchange and contributes to pulmonary hypertension. Intimal thickening of the pulmonary arteries, best seen with elastin stain, underlies pulmonary hypertension **(Fig. 8-2C)** and, at autopsy, is often associated with multiple pulmonary emboli and evidence of myocardial fibrosis.

GASTROINTESTINAL TRACT

Pathologic changes can be found at any level from the mouth to the rectum. T e lower esophagus shows prominent atrophy of the muscular layers and characteristic vascular lesions; striated muscle in the upper third of the esophagus is generally spared. Replacement of the normal intestinal tract architecture results in diminished peristaltic activity, with gastroesophageal reflux, dysmotility, and small-bowel obstruction. Chronic reflux is associated with esophageal inflammation, ulcerations, and stricture formation and may lead to Barrett's metaplasia.

KIDNEYS

In the kidneys, vascular lesions affecting the interlobular and arcuate arteries predominate. Chronic renal ischemia is associated with shrunken glomeruli. Acute scleroderma renal crisis is associated with a classic thrombotic microangiopathic pathology: reduplication of elastic lamina, marked intimal proliferation, and narrowing of the lumen in small renal arteries, commonly accompanied by thrombosis and hemolysis.

HEART

T e heart is frequently affected, with prominent involvement of the myocardium and pericardium. T e characteristic arteriolar lesions are concentric intimal hypertrophy and luminal narrowing, accompanied by contraction band necrosis reflecting ischemia-reperfusion injury and myocardial fibrosis. Fibrosis of the conduction system is common, especially at the sinoatrial node. Despite the prominent role of ischemia in SSc, the frequency of atherosclerotic coronary artery disease is comparable to the general population.

OTHER ORGANS

Synovitis may be found in early SSc; however, with disease progression, the synovium becomes fibrotic. Fibrosis of tendon sheaths and fascia produces palpable and sometimes audible tendon friction rubs. Inflammation and, in later stages, atrophy and fibrosis of the muscles are common findings. Fibrosis of the thyroid gland and of the minor salivary glands may be seen.

CLINICAL FEATURES

OVERVIEW

Virtually every organ can be clinically affected **(Table 8-4)**. Most patients with SSc can be classified as lcSSc or dcSSc (Table 8-2). Although stratification of SSc patients into diffuse and limited cutaneous subsets is useful, disease expression is far more complex, and several distinct endophenotypes exist within each subset. For example, 10–15% of patients with lcSSc develop PAH without significant ILD. Other patients have systemic features of SSc without appreciable skin involvement (SSc sine scleroderma). Unique clinical phenotypes of SSc associate with specific autoantibodies (Table 8-3). Patients with "overlap" have typical SSc features coexisting with clinical and laboratory evidence of another autoimmune disease such as polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE.

INITIAL CLINICAL PRESENTATION

T e initial presentation is quite different in the diffuse and the limited cutaneous forms of the disease. In dcSSc, the interval between Raynaud's phenomenon and onset of other disease manifestations is typically brief (weeks to months). Soft tissue swelling and intense pruritus are signs of the early inflammatory

TABLE 8-4

FREQUENCY OF CLINICAL ORGAN INVOLVEMENT: LIMITED CUTANEOUS AND DIFFUSE CUTANEOUS FORMS OF SYSTEMIC SCLEROSIS (SSC)

FEATURES	LIMITED CUTANEOUS SSC (%)	DIFFUSE CUTANEOUS SSC (%)
Skin involvement	90[a]	100
Raynaud's phenomenon	99	98
Esophageal involvement	90	80
Pulmonary fibrosis	35	65
Pulmonary arterial hypertension	15	15
Myopathy	11	23
Cardiac involvement	9	12
Scleroderma renal crisis	2	15

[a]Approximately 10% of limited cutaneous SSc patients have SSc sine scleroderma.

"edematous" phase. T e fingers, hands, distal limbs, and face are usually affected first. Diffuse skin hyperpigmentation and carpal tunnel syndrome can occur. Arthralgias, muscle weakness, fatigue, and decreased joint mobility are common. During the ensuing weeks to months, the inflammatory edematous phase evolves into the "fibrotic" phase, with skin induration associated with hair loss, reduced production of skin oils, and a decline in sweating capacity. Progressive flexion contractures of the fingers ensue. T e wrists, elbows, shoulders, hip girdles, knees, and ankles become stiff due to fibrosis of the supporting joint structures. While advancing skin involvement is the most visible manifestation of early dcSSc, important and frequently clinically silent internal organ involvement develops during this stage. T e initial 4 years from disease onset is the period of rapidly evolving pulmonary and renal damage. If organ failure does not occur during this period, the systemic process may stabilize.

Compared to dcSSc, the course of lcSSc is characteristically more indolent. In these patients, the interval between Raynaud's phenomenon and onset of manifestations such as gastroesophageal reflux, cutaneous telangiectasia, or soft tissue calcifications can be several years. On the other hand, scleroderma renal crisis and severe pulmonary fibrosis are uncommon in lcSSc. Clinically evident cardiac involvement and PAH develop in more than 15%. Overlap with keratoconjunctivitis sicca, polyarthritis, cutaneous vasculitis, and biliary cirrhosis is seen in some patients with lcSSc.

ORGAN INVOLVEMENT

RAYNAUD'S PHENOMENON

Raynaud's phenomenon, the most frequent extracutaneous complication of SSc, is characterized by episodes of reversible vasoconstriction in the fingers and toes. Vasoconstriction may also affect the tip of the nose and earlobes. Attacks are triggered by a decrease in temperature, as well as emotional stress and vibration. Typical attacks start with pallor, followed by cyanosis of variable duration. Hyperemia ensues spontaneously or with rewarming of the digit. T e progression of the three color phases reflects the underlying vasoconstriction, ischemia, and reperfusion.

As much as 3–5% of the general population has Raynaud's phenomenon. In the absence of signs or symptoms of an underlying condition, Raynaud's phenomenon is classified as primary and represents an exaggerated physiologic response to cold. Secondary Raynaud's phenomenon can occur as a complication of SSc and other connective tissue diseases, hematologic and endocrine conditions, and occupational disorders, and can complicate the use of beta blockers and anticancer drugs such as cisplatin and bleomycin. Distinguishing primary versus secondary Raynaud's phenomenon presents a diagnostic challenge. Primary Raynaud's phenomenon is supported by the following: absence of an underlying cause; a family history of Raynaud's phenomenon; absence of digital tissue necrosis, ulceration, or gangrene; and a negative ANA test. Secondary Raynaud's phenomenon tends to develop at an older age (>30 years), is clinically more severe (episodes more frequent, prolonged, and painful), and is frequently associated with ischemic digital ulcers and loss of digits **(Fig. 8-3)**. Nailfold capillaroscopy, where the cutaneous capillaries at the nail bed are viewed under a drop of grade B immersion oil using a low-power stereoscopic microscope, can be helpful in the evaluation of Raynaud's phenomenon. Primary Raynaud's phenomenon is associated with normal capillaries that appear as regularly spaced parallel vascular loops, whereas in patients with Raynaud's associated with SSc and other connective tissue diseases, nailfold capillaries are distorted with widened and irregular loops, dilated lumen, and areas of vascular "dropout." In addition to digits, cold-induced episodic Raynaud's-like vasospasm has been documented in the pulmonary, renal, gastrointestinal, and coronary circulations in SSc.



FIGURE 8-3
Digital necrosis. Sharply demarcated necrosis of the fingertip in a patient with limited cutaneous systemic sclerosis (SSc) associated with severe Raynaud's phenomenon.

SKIN FEATURES

While early-stage SSc is associated with edematous skin changes, skin thickening is the hallmark that distinguishes SSc from other connective tissue diseases. T e distribution of skin thickening is invariably symmetric and bilateral. It typically starts in the fingers and then characteristically advances from distal to proximal



FIGURE 8-4
Sclerodactyly. Note skin induration on the fingers, and fixed flexion contractures at the proximal interphalangeal joints in a patient with limited cutaneous systemic sclerosis (SSc).

extremities in an ascending fashion. The involved skin is firm, coarse, and thickened, and the extremities and trunk may be darkly pigmented. In some patients, diffuse tanning in the absence of sun exposure is a very early manifestation of skin involvement. In dark-skinned patients, vitiligo-like hypopigmentation may occur. Because pigment loss spares the perifollicular areas, the skin may have a "salt-and-pepper" appearance, most prominently on the scalp, upper back, and chest. Dermal sclerosis due to collagen accumulation obliterates hair follicles, sweat glands, and eccrine and sebaceous glands, resulting in hair loss, decreased sweating, and dry skin. Transverse creases on the dorsum of the fingers disappear **(Fig. 8-4)**. Fixed flexion contractures of the fingers cause reduced hand mobility and lead to muscle atrophy. Skin thickening in combination with fibrosis of the subjacent tendons accounts for contractures of the wrists, elbows, and knees. Thickened ridges at the neck due to firm adherence of skin to the underlying platysma muscle interfere with neck extension. The face assumes a characteristic "mauskopf" appearance with taut and shiny skin, loss of wrinkles, and occasionally an expressionless facies due to reduced mobility of the eyelids, cheeks, and mouth. Thinning of the lips with accentuation of the central incisor teeth and fine wrinkles (radial furrowing) around the mouth complete the picture. Reduced oral aperture (microstomia) interferes with eating and oral hygiene. The nose assumes a pinched, beak-like appearance.

In established SSc, the skin is firmly bound to the subcutaneous fat (tethering) and undergoes thinning and atrophy. Telangiectasias are dilated skin capillaries 2–20 mm in diameter frequently seen in lcSSc. These lesions, reminiscent of hereditary hemorrhagic telangiectasia, are prominent on the face, hands, lips, and oral mucosa **(Fig. 8-5)**. A greater number of telangiectasias



A



B

FIGURE 8-5
Cutaneous vascular changes. A. Capillary changes at the nailfold in a patient with limited cutaneous systemic sclerosis (lcSSc). B. Telangiectasia on the face.

correlates with the extent of microvascular complications, including PAH. Breakdown of atrophic skin leads to chronic ulcerations at the extensor surfaces of the proximal interphalangeal joints, the volar pads of the fingertips, and bony prominences such as the elbows and malleoli. Ulcers are painful and may become secondarily infected, resulting in osteomyelitis. Healing of ischemic fingertip ulcerations leaves characteristic fixed digital "pits." Loss of soft tissue at the fingertips due to ischemia is frequent and may be associated with striking resorption of the terminal phalanges (acro-osteolysis) **(Fig. 8-6)**.

Calcium deposits (calcinosis) in the skin and soft tissues occur in patients with lcSSc who are positive for anticentromere antibodies. The deposits, varying in size from tiny punctate lesions to large conglomerate masses, are composed of calcium hydroxyapatite crystals and can be readily visualized on plain x-rays. Frequent locations include the finger pads, palms, extensor



FIGURE 8-6
Acro-osteolysis. Note dissolution of terminal phalanges in a patient with long-standing limited cutaneous systemic sclerosis (lcSSc) and Raynaud's phenomenon.

surfaces of the forearms, and the olecranon and prepatellar bursae **(Fig. 8-7)**. They may occasionally ulcerate through the overlying skin, producing drainage of chalky white material, pain, and local inflammation. Paraspinal soft tissue calcifications may cause neurologic complications.

PULMONARY FEATURES

Pulmonary involvement is frequent in SSc and is the leading cause of death. The two principal forms are ILD and pulmonary vascular disease. Patients with SSc frequently develop some degree of both complications. Less frequent pulmonary manifestations include aspiration pneumonitis complicating chronic gastroesophageal reflux, pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis,



FIGURE 8-7
Calcinosis cutis. Note large calcific deposit breaking through the skin in a patient with limited cutaneous systemic sclerosis (lcSSc).

pleural reactions, restrictive ventilatory defect due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity. The incidence of lung cancer is increased.

Interstitial lung disease (ILD)

Evidence of ILD can be found in up to 90% of patients with SSc at autopsy and 85% by thin-section high-resolution computed tomography (HRCT). In contrast, clinically significant ILD develops in 16–43%; the frequency varies depending on the detection method used. Risk factors include male gender, African-American race, diffuse skin involvement, severe gastroesophageal reflux, and the presence of topoisomerase I autoantibodies, as well as a low forced vital capacity (FVC) or single-breath diffusing capacity of the lung for carbon monoxide (DLco) at initial presentation. In these patients, the most rapid progression in lung disease occurs early in the course of the disease (within the first 3 years), when the FVC can decline by 30% per year.

Pulmonary involvement can remain asymptomatic until it is advanced. The most common presenting respiratory symptoms—exertional dyspnea, fatigue, and reduced exercise tolerance—are subtle and slowly progressive. A chronic dry cough may be present. Physical examination may reveal "Velcro" crackles at the lung bases. Pulmonary function testing (PFT) is a sensitive method for detecting early pulmonary involvement. The most common abnormalities are reductions in FVC, total lung capacity (TLC), and DLco. A reduction in DLco that is significantly out of proportion to the reduction in lung volumes should raise suspicion for pulmonary vascular disease, but may also be due to anemia. Oxygen desaturation with exercise is common.

Chest radiography can rule out infection and other causes of pulmonary involvement, but compared to HRCT, it is relatively insensitive for detection of early ILD. HRCT shows subpleural reticular linear opacities and ground-glass opacifications, predominantly in the lower lobes, even in asymptomatic patients **(Fig. 8-8)**. Additional HRCT findings include mediastinal lymphadenopathy, pulmonary nodules, traction bronchiectasis, and uncommonly, honeycomb changes. The extent of pulmonary interstitial changes on HRCT is a predictor of mortality in SSc. Bronchoalveolar lavage (BAL) can demonstrate inflammation in the lower respiratory tract and may be useful for ruling out infection. Although an elevated proportion of neutrophils (>2%) and/or eosinophils (>3%) in the BAL fluid is correlated with more extensive lung disease on HRCT and is associated with more rapid decline in FVC and reduced survival, BAL is not useful for identifying reversible alveolitis. Lung biopsy is indicated only in patients with atypical findings on chest radiographs and should be thoracoscopically guided. The histologic pattern on

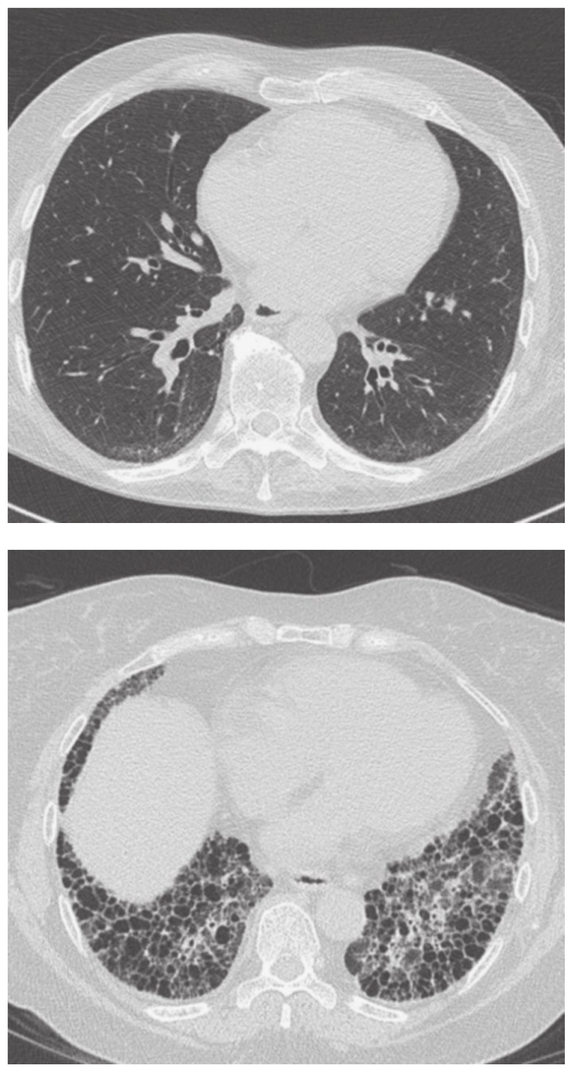


FIGURE 8-8
HRCT images of the chest from patients with systemic sclerosis. Top panel: Early interstitial lung disease. Mild changes with sub pleural reticulations and ground glass opacities in the lower lobes of the lung. Patient in supine position. Bottom panel: Extensive lung fibrosis with ground glass opacities, coarse reticular honeycombing, and traction bronchiectasis. (Courtesy of Rishi Agrawal, MD.)

lung biopsy may predict the risk of progression of ILD. The most common pattern in SSc, NSIP, carries a better prognosis than UIP.

Pulmonary Arterial Hypertension (PAH)

PAH, defined as a mean pulmonary arterial pressure ≥25 mmHg with a pulmonary capillary wedge pressure ≤15 mmHg, develops in approximately 15% of patients with SSc and can occur in association with ILD or as an isolated abnormality. The natural history of SSc-associated PAH is variable, but in many patients, it follows a downhill course with development of right heart failure. The median survival of SSc patients with untreated PAH is 1 year following diagnosis. Risk factors for PAH include limited cutaneous disease, older age at disease onset, severe Raynaud's phenomenon, and the presence of antibodies to centromere, U1-RNP, U3-RNP (fibrillarin), and B23.

The initial symptom of PAH is typically exertional dyspnea and reduced exercise capacity. With disease progression, angina, exertional near-syncope, and symptoms and signs of right-sided heart failure appear. Physical examination may show tachypnea, a prominent split S_2 heart sound, palpable right ventricular heave, elevated jugular venous pressure, and dependent edema. Doppler echocardiography provides a noninvasive method for estimating the pulmonary arterial pressure. In light of the poor prognosis of untreated PAH, all SSc patients should be screened for its presence at initial evaluation. Echocardiographic estimates of pulmonary arterial systolic pressures >40 mmHg at rest suggest PAH. Pulmonary function testing may show a reduced DLco in isolation or out of proportion with the severity of restriction. Right heart catheterization is the gold standard for diagnosing PAH. Because echocardiography can result in over- or underestimation of pulmonary arterial pressures in SSc, cardiac catheterization is always required to confirm the presence of PAH; accurately assess its severity, including the degree of right heart dysfunction; and rule out venoocclusive disease and other cardiac causes of pulmonary hypertension. Yearly echocardiographic screening for PAH is recommended in most patients with SSc; an isolated decline in DLco may also be indicative of developing PAH. Serum levels of brain natriuretic peptide (BNP) and N-terminal pro-BNP correlate with the presence and severity of PAH in SSc, as well as survival. While BNP measurements can be useful in screening for PAH and in monitoring the response to treatment, elevated BNP levels are not specific for PAH and also occur in other forms of right and left heart disease. The prognosis of SSc-associated PAH is worse, and treatment response poorer, than in idiopathic PAH.

GASTROINTESTINAL INVOLVEMENT

The gastrointestinal tract is affected in up to 90% of SSc patients with both limited and diffuse cutaneous forms of the disease. The pathologic features of atrophy of smooth muscle, intact mucosa, and obliterative small-vessel vasculopathy are similar throughout the length of the gastrointestinal tract.

UPPER GASTROINTESTINAL TRACT INVOLVEMENT

Oropharyngeal manifestations due to a combination of xerostomia, reduced oral aperture, periodontal disease, and resorption of the mandibular condyles are frequent and cause much distress. The frenulum of the tongue may be shortened. Most patients have symptoms of gastroesophageal reflux disease (GERD): heartburn, regurgitation, and dysphagia. A combination of reduced lower esophageal sphincter pressure resulting in gastroesophageal reflux, impaired esophageal clearance of refluxed gastric contents due to diminished motility in the distal two-thirds of the esophagus, and delayed gastric emptying accounts for GERD. Manometry shows

abnormal upper intestinal motility in most patients with SSc. Extraesophageal manifestations of GERD include hoarseness, chronic cough, and aspiration pneumonitis, which may aggravate underlying ILD. Chest computed tomography (CT) scan characteristically shows a dilated esophagus with intraluminal air. Endoscopy may be necessary to rule out opportunistic infections with Candida, herpes virus, and cytomegalovirus. Severe erosive esophagitis may be found on endoscopy in patients with minimal symptoms. Esophageal strictures and Barrett's esophagus may complicate chronic GERD. Because Barrett's esophagus is associated with an increased risk of adenocarcinoma, SSc patients with Barrett's esophagus need periodic endoscopy and esophageal biopsy.

Gastroparesis with early satiety, abdominal distention, and aggravated reflux symptoms is common. T e presence and severity of gastroparesis can be assessed by radionuclide gastric emptying studies. Gastric antral vascular ectasia (GAVE) in the antrum may occur. T ese subepithelial lesions, reflecting the diffuse small-vessel vasculopathy of SSc, are described as "watermelon stomach" due to their endoscopic appearance. Patients with GAVE can have recurrent episodes of gastrointestinal bleeding, resulting in chronic unexplained anemia.

LOWER GASTROINTESTINAL TRACT INVOLVEMENT

Impaired intestinal motility may result in malabsorption and chronic diarrhea secondary to bacterial overgrowth. Fat and protein malabsorption and vitamin B_{12} and vitamin D deficiency ensue, sometimes culminating in severe malnutrition. Disturbed intestinal motor function can also cause intestinal pseudo-obstruction, with symptoms of nausea and abdominal distension that are indistinguishable from those of delayed gastric emptying. Patients present with recurrent episodes of acute abdominal pain, nausea, and vomiting. Radiographic studies show acute intestinal obstruction, and the major diagnostic challenge is to differentiate pseudoobstruction, which responds to supportive care and intravenous nutritional supplementation, from mechanical obstruction.

Colonic involvement may cause severe constipation, fecal incontinence, gastrointestinal bleeding from telangiectasia, and rectal prolapse. In late-stage SSc, wide-mouth sacculations or diverticula occur in the colon, occasionally causing perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis due to air trapping in the bowel wall that may rarely rupture and cause benign pneumoperitoneum. Although the liver is rarely affected, primary biliary cirrhosis may coexist with SSc.

RENAL INVOLVEMENT: SCLERODERMA RENAL CRISIS

Scleroderma renal crisis occurs in 10–15% of patients and generally within 4 years of the onset of the disease. Prior to the advent of angiotensin-converting enzyme (ACE) inhibitors, short-term survival in scleroderma renal crisis was <10%. T e pathogenesis involves obliterative vasculopathy and luminal narrowing of the renal arcuate and interlobular arteries. Progressive reduction in renal blood flow, aggravated by vasospasm, leads to juxtaglomerular hyperplasia, increased renin secretion, and activation of angiotensin, with further renal vasoconstriction resulting in a vicious cycle that culminates in accelerated hypertension. Risk factors for scleroderma renal crisis include African-American race, male gender, and dcSSc with extensive and progressive skin involvement. Up to 50% of patients with scleroderma renal crisis have anti-RNA polymerase III antibodies. Palpable tendon friction rubs, pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High-risk patients with early SSc should be counseled to check their blood pressure daily. Patients with lcSSc or anticentromere antibodies rarely develop scleroderma renal crisis. Because there is an association between glucocorticoid use and scleroderma renal crisis, prednisone should be used in high-risk SSc patients only when absolutely required and at low doses (<10 mg/d).

Patients characteristically present with accelerated hypertension and progressive oliguric renal insuf - ciency. However, approximately 10% of patients with scleroderma renal crisis present with normal blood pressure. Normotensive renal crisis is generally associated with a poor outcome. Headache, blurred vision, and congestive heart failure may accompany elevation of blood pressure. Urinalysis typically shows mild proteinuria, granular casts, and microscopic hematuria; thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can be seen. Progressive oliguric renal failure over several days generally follows. In some cases, scleroderma renal crisis is misdiagnosed as thrombotic thrombocytopenic purpura or other forms of thrombotic microangiopathy. In these cases, a renal biopsy may be of some benefit. In addition, biopsy findings of vascular thrombosis and glomerular ischemic collapse predict poor renal outcomes. Oliguria or a creatinine >3 mg/dL at presentation predicts poor outcome, with permanent hemodialysis and high mortality. Rarely, crescentic glomerulonephritis occurs in the setting of SSc and may be associated with myeloperoxidase-specific antineutrophil cytoplasmic antibodies. Membranous glomerulonephritis may occur in patients treated with d-penicillamine.

Asymptomatic renal function impairment occurs in up to half of SSc patients. Such subclinical renal involvement is associated with other vascular manifestations of SSc and rarely progresses.

CARDIAC INVOLVEMENT

Although it is often silent, cardiac involvement in SSc is frequently detected when patients are screened with sensitive diagnostic tools. Clinically evident cardiac involvement is associated with poor outcomes. Cardiac disease in SSc may be primary or secondary to PAH, ILD, or renal involvement. It occurs more frequently in patients with dcSSc than in those with lcSSc and generally develops within 3 years of the onset of skin thickening. Clinically evident cardiac involvement in SSc is a poor prognostic factor. T e endocardium, myocardium, and pericardium may each be affected separately or together. Manifestations of pericardial involvement include acute pericarditis, pericardial effusions, constrictive pericarditis, and cardiac tamponade. Conduction system fibrosis occurs commonly and may be silent or manifested by atrial and ventricular tachycardias or heart block. Recurrent vasospasm and ischemia-reperfusion injury contribute to myocardial fibrosis, resulting in asymptomatic systolic or diastolic left ventricular dysfunction that may progress to overt heart failure. Systemic and pulmonary hypertension and lung and renal involvement may also impact on the heart. Despite the presence of widespread obliterative vasculopathy, the frequency of clinical or pathologic epicardial coronary artery disease in SSc is not increased. While conventional echocardiography has low sensitivity for detecting SSc preclinical heart involvement, newer modalities such as tissue Doppler echocardiography (TDE), cardiac magnetic resonance imaging (cMRI), thallium perfusion, and nuclear imaging (single photon emission CT [SPECT]) reveal a high prevalence of abnormal myocardial function or perfusion in SSc patients. T e serum level of N-terminal pro-BNP, a ventricular hormone, is a marker for PAH in SSc, but may also have utility as a marker of primary cardiac involvement.

MUSCULOSKELETAL COMPLICATIONS

Carpal tunnel syndrome occurs frequently and may be a presenting manifestation. Generalized arthralgia and stiffness are prominent in early disease. Mobility of small and large joints is progressively impaired, especially in dcSSc. Most commonly affected are the hands. Contractures develop at the proximal interphalangeal joints and wrists. Large joint contractures can be accompanied by tendon friction rubs, characterized by leathery crepitation that can be heard or palpated upon passive movement, that are due to extensive fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. Presence of tendon friction rubs is associated with increased risk for renal and cardiac complications and reduced survival. True joint inflammation is uncommon; however, occasional patients develop erosive polyarthritis in the hands. Muscle weakness is common and may indicate deconditioning, disuse atrophy, and malnutrition. Less commonly, inflammatory myositis indistinguishable from idiopathic polymyositis may occur. A chronic noninflammatory myopathy characterized by atrophy and fibrosis in the absence of elevated muscle enzyme levels can be seen in late-stage SSc. Bone resorption occurs most commonly in the terminal phalanges, where it causes loss of the distal tufts (acro-osteolysis) (Fig. 8-5). Resorption of the mandibular condyles can lead to bite dif culties. Osteolysis can also affect the ribs and distal clavicles.

OTHER DISEASE MANIFESTATIONS

Many SSc patients develop dry eyes and dry mouth (sicca complex). Biopsy of the minor salivary glands shows fibrosis rather than focal lymphocytic infiltration characteristic of primary Sjögren's syndrome **(Chap. 9)**. Hypothyroidism is common and generally due to fibrosis of the thyroid gland. T e frequency of macrovascular involvement, including peripheral vascular and coronary artery disease, may be increased. Whereas the central nervous system is generally spared, sensory trigeminal neuropathy due to fibrosis or vasculopathy can occur, presenting with gradual onset of pain and numbness. Pregnancy in women with SSc may be associated with an increased rate of adverse fetal outcomes. Furthermore, cardiopulmonary involvement may worsen during pregnancy, and new onset of scleroderma renal crisis has been described. Erectile dysfunction is frequent in men with SSc and may be the initial disease manifestation. Inability to attain or maintain penile erection is due to vascular insuf ciency and fibrosis.

MALIGNANCY IN SSC

Epidemiologic studies indicate an increased risk of cancer in SSc. Lung cancer and esophageal adenocarcinoma typically occur in the setting of long-standing ILD or gastroesophageal reflux disease and may be caused by chronic inflammation and repair. In contrast, breast, lung, and ovarian carcinomas and lymphomas tend to occur in close temporal association with the clinical onset of SSc, particularly in patients who have autoantibodies to RNA polymerase III. In these cases,

SSc may represent a paraneoplastic syndrome triggered by the anti-tumor immune response.

LABORATORY EVALUATION AND BIOMARKERS

A mild normocytic or microcytic anemia is frequent in patients with SSc and may indicate gastrointestinal bleeding caused by GAVE or chronic esophagitis. Macrocytic anemia may be caused by folate and vitamin B_{12} deficiency due to small-bowel bacterial overgrowth and malabsorption or by drugs such as methotrexate or alkylating agents. Microangiopathic hemolytic anemia caused by mechanical fragmentation of red blood cells during their passage through microvessels coated with fibrin or platelet thrombi is a hallmark of the thrombotic microangiopathy associated with scleroderma renal crisis. T rombocytopenia and leukopenia may indicate drug toxicity. In contrast to other connective tissue diseases, the erythrocyte sedimentation rate (ESR) is generally normal; an elevation may signal coexisting myositis or malignancy.

Antinuclear autoantibodies are present in almost all patients with SSc and can be detected at disease onset. Autoantibodies against topoisomerase I (Scl-70) and centromere are mutually exclusive and quite specific for SSc (Table 8-3). Topoisomerase I antibodies are detected in 31% of patients with dcSSc, but in only 13% of patients with lcSSc. T ey are associated with increased risk of ILD and poor outcomes. Anticentromere antibodies are detected in 38% of patients with lcSSc, but in only 2% of patients with dcSSc and rarely in patients with Raynaud's phenomenon and Sjögren's syndrome. Anticentromere antibodies in SSc are associated with PAH, but only infrequently with significant cardiac or renal involvement or ILD. Nucleolar immunofluorescence pattern on serologic testing reflects antibodies to U3-RNP (fibrillarin), T /To, or PM/Scl, whereas a speckled immunofluorescence pattern indicates antibodies to RNA polymerase III. Although antibodies to β2GPI occur in antiphospholipid antibody syndrome and are not specific for SSc, their presence in SSc is associated with an increased risk of ischemic lesions in the fingers.

DIAGNOSIS, STAGING, AND MONITORING

T e diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. T e presence of skin induration, with a characteristic symmetric distribution pattern associated with typical visceral organ manifestations, establishes the diagnosis with a high degree of certainty. Although the conditions listed in Table 8-1 can be associated with skin induration, the distribution pattern of skin lesions, together with the absence of Raynaud's phenomenon or typical visceral organ manifestations or SSc-specific autoantibodies, differentiates these conditions from SSc. Occasionally, full-thickness biopsy of the skin is required for establishing the diagnosis of scleredema, scleromyxedema, or nephrogenic systemic fibrosis. In lcSSc, a history of antecedent Raynaud's phenomenon and gastroesophageal reflux symptoms, coupled with the presence of sclerodactyly and capillary changes on nailfold capillaroscopy, often in combinations with cutaneous telangiectasia and calcinosis, helps to establish the diagnosis. T e finding of digital tip pitting scars and radiologic evidence of pulmonary fibrosis in the lower lobes are particularly helpful diagnostically. Primary Raynaud's phenomenon is a common benign condition that must be differentiated from early or limited SSc. Nailfold microscopy is particularly helpful in this situation, because in primary Raynaud's phenomenon, the nailfold capillaries are normal, whereas in SSc, capillary abnormalities, as well as serum autoantibodies, can be detected even before other disease manifestations.

Establishing the diagnosis of SSc at an early stage of the disease may be a challenge. In dcSSc, initial symptoms are often nonspecific and relate to inflammation. Patients complain of fatigue, swelling, aching, and stiffness, and Raynaud's phenomenon may initially be absent. Physical examination may reveal diffuse upper extremity edema and puffy fingers. Patients at this stage are sometimes diagnosed as early rheumatoid arthritis, SLE, myositis, or, most commonly, undifferentiated connective tissue disease. Within weeks to months, Raynaud's phenomenon and characteristic clinical features appear accompanied by advancing induration of the skin. T e presence of antinuclear and SSc-specific autoantibodies provides a high degree of diagnostic specificity. Raynaud's phenomenon with fingertip ulcerations or other evidence of digital ischemia, coupled with telangiectasia, distal esophageal dysmotility, unexplained ILD or PAH, or accelerated hypertension with renal failure in the absence of clinically evident skin induration, suggests the diagnosis of SSc sine scleroderma. T ese patients may have anticentromere antibodies.

TREATMENT Systemic Sclerosis

OVERVIEW: MANAGEMENT PRINCIPLES To date, no therapy has been shown to significantly alter the natural history of SSc. In contrast, multiple interventions are highly effective in alleviating the symptoms, slowing the progression of the

TABLE 8-5

KEY PRINCIPLES IN MANAGEMENT

- Establish early and accurate diagnosis.
- Evaluate internal organ involvement.
- Define clinical disease stage and activity.
- Tailor individualized therapy to each patient's unique needs.
- Assess treatment response, and adjust therapy as needed; monitor for disease progression and new complications.

cumulative organ damage, and reducing disability. A significant reduction in disease-related mortality has been noted during the past 25 years. In light of the marked heterogeneity in disease manifestations, organ complications, and natural history, treatment must be tailored to each individual patient's unique needs.

A thorough investigation should be undertaken at baseline. Optimal management incorporates the following principles **(Table 8-5)**: prompt and accurate diagnosis; classification and risk stratification based on clinical and laboratory evaluation; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for disease progression, activity, new complications, and response to therapy; adjusting therapy; and continuing patient education. In order to minimize irreversible organ damage, the management of life-threatening complications must be proactive, with regular screening and initiation of appropriate intervention at the earliest possible opportunity. In light of the complex and multisystemic nature of the SSc, a team-based management approach integrating multiple specialists should be pursued whenever possible. Most patients are treated with combinations of drugs that impact different aspects of the disease. We encourage patients to become familiar with the spectrum of potential complications and understand therapeutic options and natural history, and empower them to partner with their treating physicians. This requires a long-term relationship between patient and physician, with ongoing counseling and encouragement.

DISEASE-MODIFYING THERAPY: IMMUNOSUPPRESSIVE AGENTS Immunosuppressive agents used in the treatment of other autoimmune or connective tissue diseases have generally shown modest or no benefit in SSc. Glucocorticoids may alleviate stiffness and aching in early-stage dcSSc but do not influence the progression of skin or internal organ involvement, and their use is associated with an increased risk of scleroderma renal crisis. Therefore, glucocorticoids should be given only when absolutely necessary, at the lowest dose possible, and for brief periods only. The use of cyclophosphamide has been extensively studied in light of its efficacy in the treatment of vasculitis **(Chap. 11)**, SLE **(Chap. 4)**, and other autoimmune diseases **(Chap. 3)**.

Both oral and intermittent IV cyclophosphamide were shown to reduce the progression of SSc-associated ILD, with stabilization and, rarely, modest improvement of pulmonary function and HRCT findings after 1 year of treatment. Improvement in respiratory symptoms and skin induration was also noted. These beneficial effects wane upon discontinuation of therapy. The benefits of cyclophosphamide need to be balanced against its potential toxicity, including bone marrow suppression, opportunistic infections, hemorrhagic cystitis and bladder cancer, premature ovarian failure, and late secondary malignancies.

Methotrexate was associated with a modest skin improvement in small studies. Mycophenolate mofetil treatment was associated with improved skin induration in uncontrolled studies and was generally well tolerated. Small studies support the use of rituximab in SSc patients with skin involvement and ILD. The use of cyclosporine, azathioprine, extracorporeal photopheresis, thalidomide, rapamycin, imatinib, and IV immunoglobulin is currently not well supported by the literature. Intensive immune ablation using a conditioning regimen of high-dose chemotherapy with or without irradiation, followed by autologous stem cell reconstitution, has resulted in durable disease remission in some cases and is undergoing evaluation in randomized clinical trials. In light of its potential morbidity and mortality, as well as significant cost, autologous stem cell transplantation in SSc is still considered experimental.

Antifibrotic Therapy Because widespread tissue fibrosis in SSc causes progressive organ damage, drugs that interfere with the fibrotic process represent a rational therapeutic approach. d-Penicillamine has been extensively used as an antifibrotic agent. In retrospective studies, d-penicillamine stabilized and improved skin induration, prevented new internal organ involvement, and improved survival. However, a randomized controlled clinical trial in early active SSc found no difference in the extent of skin involvement between patients treated with standard-dose (750 mg/d) or very low-dose (125 mg every other day) d-penicillamine. Recent clinical trials show benefit of pirfenidone and of nintedanib in patients with idiopathic pulmonary fibrosis, with significant slowing of the loss of lung function. Whether these two new drugs will have comparable efficacy in the treatment of SSc-associated lung disease is still under investigation.

Vascular Therapy The goal of therapy is to control Raynaud's phenomenon, prevent the development and enhance the healing of ischemic complications, and slow the progression of obliterative vasculopathy. Patients should dress warmly, minimize cold exposure or stress, and avoid drugs that precipitate or exacerbate vasospastic episodes. Some patients with Raynaud's may respond to biofeedback therapy. Extended-release dihydropyridine calcium channel blockers such as nifedipine, amlodipine, or diltiazem can ameliorate Raynaud's phenomenon, but their use is often limited by side effects (palpitations, dependent edema, worsening gastroesophageal reflux). While ACE inhibitors do not reduce the frequency or severity of episodes, angiotensin II receptor blockers such as losartan are effective and generally well tolerated. Patients with Raynaud's phenomenon unresponsive to these

therapies may require the addition of α_1-adrenergic receptor blockers (e.g., prazosin), 5-phosphodiesterase inhibitors (e.g., sildenafil), serotonin reuptake inhibitors (e.g., fluoxetine), topical nitroglycerine, and intermittent infusions of IV prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic ulcers, the endothelin-1 receptor antagonist bosentan reduces the risk of new ulcers. Digital sympathectomy and local injections of botulinum type A (Botox) into the digits are options in patients with severe ischemia and impending loss of the digits. Empirical long-term therapy with statins and antioxidants may retard the progression of vascular damage and obliteration. Vasodilators such as ACE inhibitors, calcium channel blockers, and endothelin receptor blockers may also improve myocardial perfusion and left ventricular function.

TREATMENT OF GASTROINTESTINAL COMPLICATIONS Because oral problems including decreased oral aperture, decreased saliva production, gum recession, and periodontal disease leading to teeth loss are common, regular dental care is recommended. Gastroesophageal reflux is very common and may occur in the absence of symptoms; therefore all patients with SSc should be treated. Patients should be instructed to elevate the head of the bed, eat frequent small meals, and avoid oral intake before bedtime. Proton pump inhibitors reduce acid reflux and may need to be given in relatively high doses. Prokinetic agents such as domperidone may be helpful, especially if delayed gastric emptying is present. Episodic gastrointestinal bleeding from gastric antral vascular ectasia (watermelon stomach) may be amenable to treatment with endoscopic laser photocoagulation, although recurrence can occur. Bacterial overgrowth due to small-bowel dysmotility causes abdominal bloating and diarrhea and may lead to malabsorption and severe malnutrition. Treatment with short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and tetracycline can eradicate bacterial overgrowth. Parenteral hyperalimentation is indicated if malnutrition develops. Chronic hypomotility of the small bowel may respond to octreotide, but pseudo-obstruction is difficult to treat. Fecal incontinence, a frequently underreported complication of SSc, may respond to anti-diarrheal medication and biofeedback therapy.

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION (PAH) In patients with SSc, PAH carries an extremely poor prognosis and accounts for 30% of deaths. Because PAH is asymptomatic until advanced, patients with SSc should be screened for its presence at initial evaluation, and on a yearly basis thereafter. Treatment is generally started with an oral endothelin-1 receptor antagonist such as bosentan or a phosphodiesterase type 5 inhibitor such as sildenafil. Patients may also require diuretics and digoxin when appropriate. If hypoxemia is documented, supplemental oxygen should be prescribed in order to avoid hypoxia-induced secondary pulmonary vasoconstriction. Prostacyclin analogues such as epoprostenol or treprostinil can be given by continuous IV or SC infusion, or via intermittent nebulized inhalations. Combination therapy with different classes of agents, such as an endothelin-1 antagonist and a phosphodiesterase inhibitor, is often necessary. Lung transplantation remains an option for selected patients who fail medical therapy.

TREATMENT OF RENAL CRISIS Scleroderma renal crisis is a medical emergency. Since the outcome is largely determined by the extent of renal damage present at the time that aggressive therapy is initiated, prompt recognition of impending or early scleroderma renal crisis is essential, and efforts should be made to avoid its occurrence. High-risk SSc patients with early disease, extensive and progressive skin involvement, tendon friction rubs, and anti-RNA polymerase III antibodies should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids should be used only when absolutely necessary and at low doses. Patients presenting with scleroderma renal crisis should be immediately hospitalized. Once other causes of renal disease are excluded, treatment should be started promptly with titration of short-acting ACE inhibitors, with the goal of achieving rapid normalization of the blood pressure. In patients with hypertension persisting despite ACE inhibitor therapy, addition of angiotensin II receptor blockers, calcium channel blockers, and direct renin inhibitors should be considered. Anecdotal evidence indicates responses to endothelin-1 receptor blockers and prostacyclins. Up to two-thirds of patients with scleroderma renal crisis go on to dialysis. T e outcome of scleroderma renal crisis is worse in patients with antibodies to topoisomerase I compared to those with antibodies to RNA polymerase III. Substantial renal recovery can occur following scleroderma renal crisis, and dialysis can be discontinued, in 30–50% of the patients. Kidney transplantation is appropriate for those unable to discontinue dialysis after 2 years. Survival of transplanted SSc patients is comparable to that of patients with other connective tissue diseases, and recurrence of renal crisis is rare.

Skin Care Because skin involvement in SSc is never life-threatening and because it stabilizes and may even regress spontaneously, over time, the management of SSc should not be dictated by its cutaneous manifestations. The inflammatory symptoms of early skin involvement can be controlled with antihistamines and cautious short-term use of low-dose glucocorticoids (<5 mg/d of prednisone). Retrospective studies have shown that d-penicillamine reduced the extent and progression of skin induration; however, these benefits could not be substantiated in a controlled prospective trial. Cyclophosphamide and methotrexate have modest effects on skin induration. Because the skin is dry, the use of hydrophilic ointments and bath oils is encouraged. Regular skin massage is helpful. Telangiectasia may present a cosmetic problem, especially on the face. Treatment with pulsed dye laser may have short-term benefit. Ischemic digital ulcers should be protected by occlusive dressing to promote healing and prevent infection. Infected skin

ulcers are treated with topical antibiotics. Surgical debridement may be indicated. No therapy has been shown to be effective in preventing the formation of calcific soft tissue deposits or promoting their dissolution.

TREATMENT OF MUSCULOSKELETAL COMPLICATIONS Arthralgia and joint stiffness are common and distressing manifestations most prominent in early-stage disease. Short courses of nonsteroidal anti-inflammatory agents, weekly methotrexate, and cautious use of low-dose corticosteroids may alleviate these symptoms. Physical and occupational therapy can be effective for maintaining musculoskeletal function and improving long-term outcomes.

COURSE

T e natural history of SSc is highly variable and dif - cult to predict, especially in early stages of the disease, when the specific subset—diffuse or limited cutaneous form—is not clear. Patient with dcSSc tend to have a more rapidly progressive course and worse prognosis than those with lcSSc.

In dcSSc, inflammatory symptoms such as fatigue, edema, arthralgia, and pruritus tend to subside, and the extent of skin thickening reaches a plateau at 2–4 years after disease onset, followed by slow regression. It is during the early edematous/inflammatory stage, generally lasting <3 years, that important visceral organ involvement occurs. While existing visceral organ involvement, such as pulmonary fibrosis, may progress even after skin involvement peaks, new organ involvement is rare. Scleroderma renal crisis almost invariably occurs within the first 4 years of disease. In late-stage disease (>6 years), the skin is usually soft and atrophic. Skin regression characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunks followed by proximal and finally distal extremities; however, sclerodactyly and finger contractures generally persist. Relapse or recurrence of skin thickening after the peak of skin involvement has been reached is uncommon. Patients with lcSSc follow a clinical course that is markedly different than that of dcSSc. Raynaud's phenomenon typically precedes other disease manifestations by years or even decades. Visceral organ complications such as PAH and ILD generally develop late and progress slowly.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death. Age- and gender-adjusted mortality rates are fivefold to eightfold higher compared to the general population, and more than half of all patients with SSc die from their disease. In one population-based study of SSc, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survival rates are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survival rates are 90% and 75%, respectively. T e prognosis correlates with the extent of skin involvement, which itself is a surrogate for visceral organ involvement. Major causes of death are PAH, pulmonary fibrosis, gastrointestinal involvement, and cardiac disease. Scleroderma renal crisis is associated with a 30% 3-year mortality. Lung cancer and excess cardiovascular deaths also contribute to increased mortality. Markers of poor prognosis include male gender, African-American race, older age at disease onset, extensive skin thickening with truncal involvement, palpable tendon friction rubs, and evidence of significant or progressive visceral organ involvement. Laboratory predictors of increased mortality at initial evaluation include an elevated ESR, anemia, proteinuria and anti–topoisomerase I antibodies. In one study, SSc patients with extensive skin involvement, lung vital capacity <55% predicted, significant gastrointestinal involvement (pseudoobstruction or malabsorption), evidence of cardiac involvement (arrhythmias or congestive heart failure), or scleroderma renal crisis had a cumulative 9-year survival <40%. T e severity of PAH is strongly associated with mortality, and SSc patients who had a mean pulmonary arterial pressure ≥45 mmHg had a 33% 3-year survival. T e advent of ACE inhibitors in scleroderma renal crisis had a dramatic impact on survival, increasing from <10% at 1 year in the pre–ACE inhibitor era to >70% 3-year survival at the present time. Moreover, 10-year survival in SSc has improved from <60% in the 1970s to >66–78% in the 1990s, a trend that reflects both earlier detection and better management of complications.

LOCALIZED SCLERODERMA

T e term scleroderma is commonly used to describe a group of localized skin disorders (Table 8-1). T ese occur more commonly in children than in adults. In contrast to SSc, localized scleroderma is rarely complicated by Raynaud's phenomenon or significant internal organ involvement. Morphea presents as solitary or multiple circular patches of thickened skin or, rarely, as widespread induration (generalized or pansclerotic morphea); the fingers are spared. Linear scleroderma—streaks of thickened skin, typically in one or both lower extremities—may affect the subcutaneous tissues, leading to fibrosis and atrophy of supporting structures, muscle, and bone. In children, the growth of affected long bones can be retarded. When linear scleroderma lesions cross joints, significant contractures can develop.

MIXED CONNECTIVE TISSUE DISEASE

Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). T is overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. T e characteristic initial presentation is Raynaud's phenomenon associated with puffy fingers and myalgia. Gradually, lcSSc features of sclerodactyly, calcinosis, and cutaneous telangiectasia develop. Skin rashes suggestive of SLE (malar rash, photosensitivity) or of dermatomyositis (heliotrope rash on the eyelids, erythematous rash on the knuckles) occur. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or secondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren's syndrome, and renal disease, especially membranous glomerulonephritis. Laboratory evaluation indicates features of inflammation with elevated ESR and hypergammaglobulinemia. While anti-U1RNP antibodies are detected in the serum in high titers, SSc-specific autoantibodies are not found. In contrast to SSc, patients with MCTD often show a good response to treatment with glucocorticoids, and the long-term prognosis is better than that of SSc. Whether MCTD is a truly distinct entity or is, rather, a subset of SLE or SSc remains controversial.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis is a rare idiopathic disorder associated with induration of the skin that generally develops rapidly. Adults are primarily affected. T e skin has a coarse cobblestone "peau d'orange" appearance. In contrast to SSc, internal organ involvement is rare, and Raynaud's phenomenon and SSc-associated autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness excisional biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia and is generally required for diagnosis. Inflammation and eosinophil infiltration in the fascia are variably present. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. In some patients, eosinophilic fasciitis occurs in association with, or preceding, myelodysplastic syndromes or multiple myeloma. Treatment with glucocorticoids leads to prompt resolution of the eosinophilia. In contrast, skin changes generally show slow and variable improvement. T e prognosis of patients with eosinophilic fasciitis is good.

CHAPTER 9

SJÖGREN'S SYNDROME

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DEFINITION, INCIDENCE, AND PREVALENCE

Sjögren's syndrome is a chronic, slowly progressive autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia and dry eyes. Approximately one-third of patients present with systemic manifestations; a small but significant number of patients develop malignant lymphoma. T e disease presents alone (primary Sjögren's syndrome) or in association with other autoimmune rheumatic diseases (secondary Sjögren's syndrome) **(Table 9-1)**.

Middle-aged women (female-to-male ratio, 9:1) are primarily affected, although Sjögren's syndrome may occur at any age, including childhood. T e prevalence of primary Sjögren's syndrome is ~0.5–1%, while 30% of patients with autoimmune rheumatic diseases suffer from secondary Sjögren's syndrome.

PATHOGENESIS

Sjögren's syndrome is characterized by both lymphocytic infiltration of the exocrine glands and B lymphocyte hyperreactivity. An oligomonoclonal B cell process, which is characterized by cryoprecipitable monoclonal immunoglobulins (IgM?) with rheumatoid factor activity, is evident in up to 25% of patients.

Sera from patients with Sjögren's syndrome often contain autoantibodies to non-organ-specific antigens such as immunoglobulins (rheumatoid factors) and extractable nuclear and cytoplasmic antigens (Ro/SS-A, La/SS-B). Ro/SS-A autoantigen consists of two polypeptides (52 and 60 kDa, respectively) in conjunction with cytoplasmic RNAs, whereas the 48-kDa La/SS-B protein is bound to RNA III polymerase transcripts. Autoantibodies to Ro/SS-A and La/SS-B antigens are usually detected at the time of diagnosis and are associated with earlier disease onset, longer disease duration, salivary gland enlargement, and more intense lymphocytic infiltration of minor salivary glands.

T e major infiltrating cells in the affected exocrine glands are activated T and B lymphocytes. T cells predominate in mild lesions, whereas B cells are dominant in more severe lesions. Macrophages and dendritic cells also are found. T e number of macrophages positive for interleukin (IL) 18 has been shown to correlate with parotid gland enlargement and low levels of the C4 component of complement, both of which are adverse predictors for lymphoma development.

Ductal and acinar epithelial cells appear to play a significant role in the initiation and perpetuation of autoimmune injury. T ese cells (1) express class II major histocompatibility complex (MHC) molecules, costimulatory molecules, and abberant expression of intracellular autoantigens on cell membranes and thus are able to provide signals essential for lymphocytic activation; (2) inappropriately produce proinflammatory cytokines and lymphoattractant chemokines necessary for sustaining the autoimmune lesion and allowing progression to more sophisticated ectopic germinal center formation, which occurs in one-fifth of patients; and (3) express functional receptors of innate immunity, particularly Toll-like receptors (TLRs) 3, 7, and 9, that may account for the perpetuation of the autoimmune response.

Both infiltrating T and B cells have a tendency to be resistant to apoptosis. Levels of B cell–activating factor (BAFF) have been found to be elevated in patients with Sjögren's syndrome, especially those with hypergammaglobulinemia, and probably accounts for this antiapoptotic effect. Glandular epithelial cells seem to have an active role in the production of BAFF, which may be expressed and secreted after stimulation with type I interferon as well as with viral or synthetic double-stranded RNA. T e triggering factor for epithelial activation appears to be a persistent enteroviral infection (possibly with coxsackievirus strains). Type I and type II interferon signatures have been described in ductal epithelial cells and T cells, respectively; their detection

TABLE 9-1

ASSOCIATION OF SJÖGREN'S SYNDROME WITH OTHER AUTOIMMUNE DISEASES
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Primary biliary cirrhosis
Vasculitis
Chronic active hepatitis

implies that interferons exert direct and cross-regulating effects on the pathogenic process.

A defect in cholinergic activity mediated through the M3 receptor and redistribution of the water-channel protein aquaporin 5, both leading to neuroepithelial dysfunction and diminished glandular secretions, have been proposed.

Molecular analysis of human leukocyte antigen (HLA) class II genes has revealed that Sjögren's syndrome, regardless of the patient's ethnic origin, is highly associated with the HLA DQA1□0501 allele. Genome-wide association studies have disclosed an increased prevalence of single-nucleotide polymorphisms in genes of IRF-5 and STAT-4, which participate in the activation of the type I interferon pathway.

CLINICAL MANIFESTATIONS

T e majority of patients with Sjögren's syndrome have symptoms related to diminished lacrimal and salivary gland function. In most patients, the primary syndrome runs a slow and benign course. T e initial manifestations can be mucosal or nonspecific dryness, and 8–10 years may elapse from the initial symptoms to full-blown development of the disease.

T e principal oral symptom of Sjögren's syndrome is dryness (xerostomia). Patients report dif culty in swallowing dry food, an inability to speak continuously, a burning sensation, an increase in dental caries, and problems in wearing complete dentures. Physical examination shows a dry, erythematous, sticky oral mucosa. T ere is atrophy of the filiform papillae on the dorsum of the tongue, and saliva from the major glands is either not expressible or cloudy. Enlargement of the parotid or other major salivary glands occurs in two-thirds of patients with primary Sjögren's syndrome but is uncommon in those with the secondary syndrome. Diagnostic tests include sialometry, sialography, and scintigraphy. Newer imaging techniques, including ultrasound, MRI, and magnetic resonance sialography of the major salivary glands, are also being used. Biopsy of the labial minor salivary gland permits histopathologic confirmation of focal lymphocytic infiltrates.

Ocular involvement is the other major manifestation of Sjögren's syndrome. Patients usually describe a sandy or gritty feeling under the eyelids. Other symptoms include burning, accumulation of secretions in thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue, and increased photosensitivity. T ese symptoms, which define keratoconjunctivitis sicca, are attributed to the destruction of corneal and bulbar conjunctival epithelium. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer I test and determination of tear composition, with assessment of tear breakup time or tear lysozyme content. Slit-lamp examination of the cornea and conjunctiva after rose bengal staining reveals punctuate corneal ulcerations and attached filaments of corneal epithelium.

Involvement of other exocrine glands, which occurs less frequently, includes a decrease in mucous gland secretions of the upper and lower respiratory tree, resulting in dry nose, throat, and trachea (xerotrachea). In addition, diminished secretion of the exocrine glands of the gastrointestinal tract leads to esophageal mucosal atrophy, atrophic gastritis, and subclinical pancreatitis. Dyspareunia due to dryness of the external genitalia and dry skin also may occur.

Extraglandular (systemic) manifestations are seen in one-third of patients with Sjögren's syndrome **(Table 9-2)** but are very rare in patients whose Sjögren's syndrome is associated with rheumatoid arthritis. Patients with primary Sjögren's syndrome more often report easy fatigability, low-grade fever, Raynaud's phenomenon, myalgias, and arthralgias. Most patients with primary Sjögren's syndrome experience at least one episode of non-erosive arthritis during the course of their disease. Manifestations of pulmonary involvement are frequently evident histologically but are rarely important clinically. Dry cough is the major manifestation that is attributed to small airway disease. Renal involvement includes interstitial nephritis, clinically manifested by hyposthenuria and renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. Glomerulonephritis is a rare finding that occurs in patients with mixed cryoglobulinemia or with systemic lupus erythematosus overlapping with Sjögren's syndrome. Vasculitis affects small and medium-sized vessels. T e most common clinical features are purpura, recurrent urticaria, skin ulcerations, glomerulonephritis, and mononeuritis multiplex.

Different autoantibodies may determine the clinical expression of the disease. Patients positive for anticentromere autoantibody present with a clinical picture similar to that of limited scleroderma **(Chap. 8)**. Antimitochondrial antibodies may connote liver involvement

TABLE 9-2

PREVALENCE OF EXTRAGLANDULAR MANIFESTATIONS IN PRIMARY SJÖGREN'S SYNDROME

CLINICAL MANIFESTATION	PERCENT	REMARKS
Arthralgias/arthritis	60	Usually non-erosive, leading to Jaccoud's arthropathy.
Raynaud's phenomenon	37	In one-third of patients, precedes sicca manifestations.
Lymphadenopathy	14	Lymphoma should be excluded.
Lung involvement	14	Small airway disease is the predominant pathology.
Vasculitis	11	The most common clinical manifestation is cutaneous palpable purpura.
Kidney involvement	9	Interstitial kidney disease is usually asymptomatic. Glomerulonephritis is associated with cryoglobulinemia.
Liver involvement	6	Primary biliary cirrhosis stage I.
Lymphoma	6	Glandular MALT[a] lymphoma is most common.
Peripheral neuropathy	2	Polyneuropathy, either sensory or sensorimotor.
Myositis	1	Sporadic causes of myositis and inclusion body myositis have been reported.

[a]Mucosa-associated lymphoid tissue.

in the form of primary biliary cirrhosis. Autoantibodies to 21-hydroxylate have recently been described in almost 20% of patients; their presence is associated with a blunted adrenal response.

Central nervous system involvement is rarely recognized. A few cases of myelitis associated with antibody to aquaporin 4 have been described.

Lymphoma is a well-known manifestation of Sjögren's syndrome that usually presents later in the illness. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, low C4 complement levels, and ectopic germinal centers in minor salivary gland biopsy samples are manifestations suggesting the development of lymphoma. It is interesting that the same risk factors account for glomerulonephritis and lymphoma and that these risk factors are the ones that confer increased mortality risk. Most lymphomas are extranodal, low-grade marginal-zone B cell lymphomas and are usually detected incidentally during evaluation of the labial biopsy. T e affected lymph nodes are usually peripheral. Survival rates are decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade.

Routine laboratory tests in Sjögren's syndrome reveal mild normochromic, normocytic anemia. An elevated erythrocyte sedimentation rate is found in ~70% of patients.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Primary Sjögren's syndrome is diagnosed if (1) the patient presents with eye and/or mouth dryness, (2) eye tests disclose keratoconjunctivitis sicca, (3) mouth evaluation reveals the classic manifestations of the syndrome, and/or (4) the patient's serum reacts with Ro/SS-A and/or La/SS-B autoantigens. Labial biopsy is needed when the diagnosis is uncertain or to rule out other conditions that may cause dry mouth or eyes or parotid gland enlargement **(Tables 9-3 and 9-4)**. Validated diagnostic criteria have been established by a European study and have now been further improved by a European-American study group **(Table 9-5)**. Hepatitis C virus infection should be ruled out since, apart from serologic tests, the clinicopathologic picture is almost identical to that of Sjögren's syndrome. Enlargement of major salivary glands, particularly in seronegative patients, should raise the suspicion of IgG4-related syndrome, which may present also as chronic pancreatitis, interstitial nephritis, retroperitoneal fibrosis, and aortitis.

TREATMENT Sjögren's Syndrome

Treatment of Sjögren's syndrome is aimed at symptom relief and limitation of the damaging local effects of chronic xerostomia and keratoconjunctivitis sicca through substitution for or stimulation of the missing secretions **(Fig. 9-1)**.

To replace deficient tears, several ophthalmic preparations are readily available (hydroxypropyl methylcellulose; polyvinyl alcohol; 0.5% methylcellulose; Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended. Certain drugs that may decrease lacrimal and salivary secretions, such as diuretics, antihypertensive drugs, anticholinergics, and antidepressants, should be avoided.

For xerostomia, the best replacement is water. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, orally administered pilocarpine (5 mg thrice daily) or cevimeline (30 mg thrice daily) appears to improve sicca manifestations, and both are well tolerated. Hydroxychloroquine (200 mg) is helpful for arthralgias and mild arthritis.

TABLE 9-3

DIFFERENTIAL DIAGNOSIS OF SICC A SYMPTOMS

XEROSTOMIA	DRY EYE	BILATERAL PAROTID GLAND ENLARGEMENT
Viral infections	Inflammation	Viral infections
Drugs	Stevens-Johnson syndrome	Mumps
Psychotherapeutic	Pemphigoid	Influenza
Parasympatholytic	Chronic conjunctivitis	Epstein-Barr virus
Antihypertensive	Chronic blepharitis	Coxsackievirus A
Psychogenic origin	Sjögren's syndrome	Cytomegalovirus
Irradiation	Toxicity	HIV, HCV
Diabetes mellitus	Burns	Sarcoidosis
Trauma	Drugs	IgG4 syndrome
Sjögren's syndrome	Neurologic conditions	Sjögren's syndrome
Amyloidosis	Impaired lacrimal gland function	Metabolic disorders
	Impaired eyelid function	Diabetes mellitus
	Miscellaneous	Hyperlipoproteinemias
	Trauma	Chronic pancreatitis
	Hypovitaminosis A	Hepatic cirrhosis
	Blink abnormality	Endocrine
	Anesthetic cornea	Acromegaly
	Lid scarring	Gonadal hypofunction
	Epithelial irregularity	

TABLE 9-4

DIFFERENTIAL DIAGNOSIS OF SJÖGREN'S SYNDROME

HIV INFECTION AND SICCA SYNDROME	SJÖGREN'S SYNDROME	SARCOIDOSIS
Predominant in young males	Predominant in middle-aged women	No age or sex preference
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of autoantibodies	Lack of autoantibodies to Ro/SS-A and/or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and DRw52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV

TABLE 9-5

REVISED INTERNATIONAL CLASSIFICATION CRITERIA FOR SJÖGREN'S SYNDROME[a,b,c]

I. Ocular symptoms: a positive response to at least one of three validated questions.
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than three times a day?

II. Oral symptoms: a positive response to at least one of three validated questions.
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrent or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry foods?

III. Ocular signs: objective evidence of ocular involvement defined as a positive result to at least one of the following two tests:
   1. Shirmer's I test, performed without anesthesia (≤5 mm in 5 min)
   2. Rose Bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands focal lymphocytic sialoadenitis, with a focus score ≥1.

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result to at least one of the following diagnostic tests:
   1. Unstimulated whole salivary flow (≤1.5 mL in 15 min)
   2. Parotid sialography
   3. Salivary scintigraphy

VI. Antibodies in the serum to Ro/SS-A or La/SS-B antigens, or both.

[a]Exclusion criteria: past head and neck radiation treatment, hepatitis C infection, AIDS, preexisting lymphoma, sarcoidosis, graft-versus-host disease, use of anticholinergic drugs.

[b]Primary Sjögren's syndrome: any four of the six items, as long as item IV (histopathology) or VI (serology) is positive; or any three of the four objective-criteria items (III, IV, V, VI).

[c]In patients with a potentially associated disease (e.g., another well-defined connective tissue disease), the presence of item I or item II plus any two from among items III, IV, and V may be considered indicative of secondary Sjögren's syndrome.

Source: From C Vitali et al: Ann Rheum Dis 61:554, 2002. ©2002 with permission from BMJ Publishing Group Ltd.

Patients with renal tubular acidosis should receive sodium bicarbonate by mouth (0.5-2 mmol/kg in four divided doses). Glucocorticoids (1 mg/kg per day) and/or immunosuppressive agents (e.g., cyclophosphamide) are indicated only for the treatment of systemic vasculitis. Anti-tumor necrosis factor agents are ineffective. Monoclonal antibody to CD20 appears to be effective in patients with systemic disease, particularly in those with vasculitis, arthritis, and fatigability. Combination of anti-CD-20 with a classic CHOP regimen (cyclosporine, adriamycin [hydroxydaunorubicin], vincristine [oncovin], and prednisone) leads to increased survival rates among patients with high-grade lymphomas.

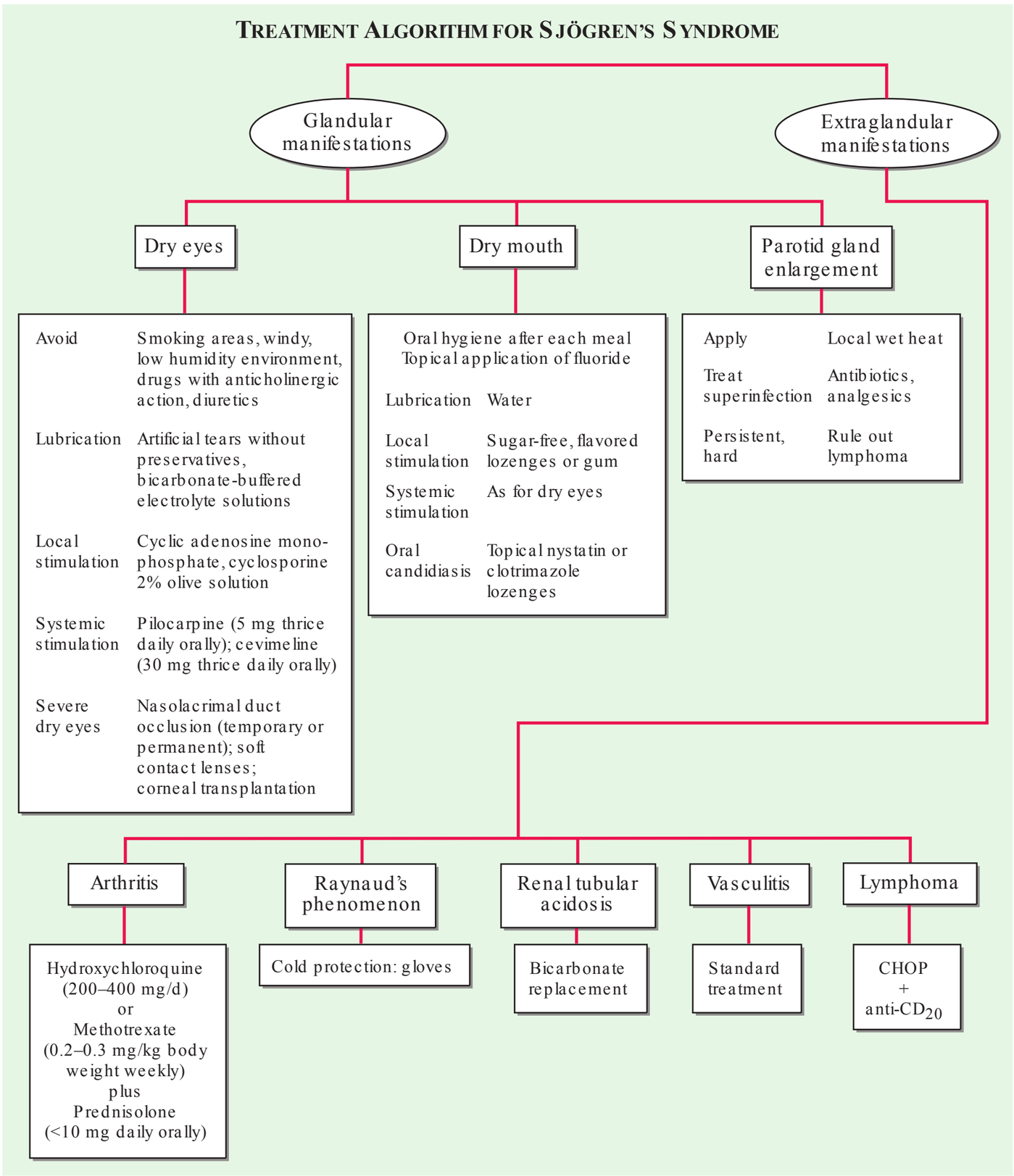


FIGURE 9-1
Treatment algorithm for Sjögren's syndrome. CHOP, cyclophosphamide, adriamycin (hydroxydaunorubicin), vincristine (oncovin), and prednisone.

CHAPTER 10

THE SPONDYLOARTHRITIDES

Joel D. Taurog ■ John D. Carter

The spondyloarthritides are a group of overlapping disorders that share certain clinical features and genetic associations. These disorders include ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis and spondylitis, enteropathic arthritis and spondylitis, juvenile-onset spondyloarthritis (SpA), and undifferentiated SpA. The similarities in clinical manifestations and genetic predisposition suggest that these disorders share pathogenic mechanisms.

ANKYLOSING SPONDYLITIS

AS is an inflammatory disorder of unknown cause that primarily affects the axial skeleton; peripheral joints and extraarticular structures are also frequently involved. The disease usually begins in the second or third decade; male-to-female prevalence is between 2:1 and 3:1. The term axial spondyloarthritis is coming into common use, supported by criteria formulated in 2009 **(Table 10-1)**. This classification includes both definite AS and early stages that do not yet meet classical criteria for AS, but it probably also includes other conditions with a different natural history.

EPIDEMIOLOGY

AS shows a striking correlation with the histocompatibility antigen HLA-B27 and occurs worldwide roughly in proportion to the prevalence of B27. In North American whites, the prevalence of B27 is 7%, whereas it is 90% in patients with AS, independent of disease severity.

In population surveys, AS is present in 1–6% of adults inheriting B27, whereas the prevalence is 10–30% among B27+ adult first-degree relatives of AS probands. Concordance rate in identical twins is about 65%. Susceptibility to AS is determined largely by genetic factors, with B27 comprising less than one-half of the genetic component. Genome-wide single-nucleotide polymorphism (SNP) analysis has identified over 30 additional susceptibility alleles.

PATHOLOGY

Sacroiliitis is often the earliest manifestation of AS. Knowledge of its pathology comes from both biopsy and autopsy studies that cover a range of disease durations. Synovitis and myxoid marrow represent the earliest changes, followed by pannus and subchondral granulation tissue. Marrow edema, enthesitis, and chondroid differentiation are also found. Macrophages, T cells, plasma cells, and osteoclasts are prevalent. Eventually the eroded joint margins are gradually replaced by fibrocartilage regeneration and then by ossification. The joint may become totally obliterated.

In the spine, the specimens studied have either been surgically resected in advanced disease or taken from autopsies. There is inflammatory granulation tissue in the paravertebral connective tissue at the junction of annulus fibrosus and vertebral bone, and in some cases along the entire outer annulus. The outer annular fibers are eroded and eventually replaced by bone, forming the beginning of a syndesmophyte, which then grows by continued endochondral ossification, ultimately bridging the adjacent vertebral bodies. Ascending progression of this process leads to the "bamboo spine." Other lesions in the spine include diffuse osteoporosis (loss of trabecular bone despite accretion of periosteal bone), erosion of vertebral bodies at the disk margin, "squaring" or "barreling" of vertebrae, and inflammation and destruction of the disk-bone border. Inflammatory arthritis of the apophyseal (facet) joints is common, with synovitis, inflammation at the bony attachment of the joint capsule, and subchondral bone marrow granulation tissue. Erosion of joint cartilage by pannus is often followed by bony ankylosis. This is may precede formation of syndesmophytes bridging the

TABLE 10-1

ASAS CRITERIA FOR CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS (TO BE APPLIED FOR PATIENTS WITH BACK PAIN ≥3 MONTHS AND AGE OF ONSET <45 YEARS)[a]

SACROILIITIS ON IMAGING PLUS ≥1 SpA FEATURE	OR	HLA-B27 PLUS ≥2 OTHER SpA FEATURES
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliitis[b] and/or • Definite radiographic sacroiliitis according to modified New York criteria[c]		SpA features • Inflammatory back pain[d] • Arthritis[e] • Enthesitis (heel)[f] • Anterior uveitis[g] • Dactylitis[e] • Psoriasis[e] • Crohn's disease or ulcerative colitis[e] • Good response to NSAIDs[h] • Family history of SpA[i] • HLA-B27 • Elevated CRP[j]

[a]Sensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%.
[b]Bone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image.
[c]Bilateral grade ≥2 or unilateral grade 3 or 4.
[d]See text for criteria.
[e]Past or present, diagnosed by a physician.
[f]Past or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia.
[g]Past or present, confirmed by an ophthalmologist.
[h]Substantial relief of back pain at 24–48 h after a full dose of NSAID.
[i]First- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD).
[j]After exclusion of other causes of elevated CRP.
Abbreviations: ASAS, Assessment of Spondyloarthritis International Society; CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.
Source: From M Rudwaleit et al: Ann Rheum Dis 68:777, 2009. Copyright 2009, with permission from BMJ Publishing Group Ltd.

adjacent disks. Bone mineral density is diminished in the spine and proximal femur early in the course of the disease.

Peripheral synovitis in AS shows marked vascularity, which is also evident as tortuous macrovascularity seen during arthroscopy. Lining layer hyperplasia, lymphoid infiltration, and pannus formation are also found. Central cartilaginous erosions caused by proliferation of subchondral granulation tissue are common. It should be emphasized that the characteristics of peripheral arthritis in AS and other forms of SpA are similar, and distinct from those of rheumatoid arthritis.

Inflammation in the fibrocartilaginous enthesis, the region where a tendon, ligament, or joint capsule attaches to bone, is a characteristic lesion in AS and other SpAs, both at axial and peripheral sites. Enthesitis is associated with prominent edema of the adjacent bone marrow and is often characterized by erosive lesions that eventually undergo ossification.

Subclinical intestinal inflammation has been found in the colon or distal ileum in a majority of patients with SpA. The histology is described under "Enteropathic Arthritis" on p. 154.

PATHOGENESIS

The pathogenesis of AS is immune-mediated, but there is little direct evidence for antigen-specific autoimmunity, and there is evidence to suggest more of an autoinflammatory pathogenesis. Uncertainty remains regarding the primary site of disease initiation. The dramatic response of the disease to therapeutic blockade of tumor necrosis factor α (TNF-α) indicates that this cytokine plays a central role in the immunopathogenesis of AS. Other genes related to TNF pathways show association with AS, including TNFRSF1A, LTBR, and TBKBP1. More recent evidence strongly implicates the interleukin (IL) 23/IL-17 cytokine pathway in AS pathogenesis. At least five genes in this pathway show association with AS, including IL23R, PTER4, IL12B, CARD9, and TYK2. All of these genes are also associated with inflammatory bowel disease (IBD), and three of them are associated with psoriasis. Serum levels of IL-23 and IL-17 are elevated in AS patients. Mice expressing high levels of IL-23 show spontaneous infiltration in the entheses of CD3+CD4–CD8– cells bearing IL-23 receptors and producing IL-17 and IL-22. This finding suggests the possibility that site-specific innate immune cells may play a critical role in the anatomic specificity of the lesions. Mast cells and, to a lesser extent, neutrophils appear to be the major IL-17-producing cells in peripheral arthritis, whereas neutrophils producing IL-17 are prominent in apophyseal joints. High levels of circulating γδ T cells expressing IL-23 receptors and producing IL-17 have been found in AS patients.

Other associated genes encode other cytokines or cytokine receptors (IL6R, IL1R1, IL1R2, IL7R, IL27), transcription factors involved in the differentiation of immune cells (RUNX3, EOMES, BACH2, NKX2-3, TBX21), or other molecules involved in activation or regulation of immune or inflammatory responses (FCGR2A, ZMIZ1, NOS2, ICOSLG).

The inflamed sacroiliac joint is infiltrated with CD4+ and CD8+ T cells and macrophages and shows high levels of TNF-α, particularly early in the disease. Abundant transforming growth factor β (TGF-β) has been found in more advanced lesions. Peripheral synovitis in AS and the other spondyloarthritides is characterized by neutrophils, macrophages expressing CD68 and CD163, CD4+ and CD8+ T cells, and B cells. There is prominent staining for intercellular adhesion

molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 3 (MMP-3), and myeloid-related proteins 8 and 14 (MRP-8 and MRP-14). Unlike rheumatoid arthritis (RA) synovium, citrullinated proteins and cartilage gp39 peptide–major histocompatibility complexes (MHCs) are absent. However, citrullinated proteins can be seen in the circulation.

No specific event or exogenous agent that triggers the onset of disease has been identified, although overlapping features with reactive arthritis and IBD and the involvement of the IL-23/IL-17 pathway suggest that enteric bacteria may play a role, and microdamage from mechanical stress at enthesial sites has also been implicated.

It is firmly established that HLA-B27 plays a direct role in AS pathogenesis, but its precise role at the molecular level remains unresolved. Rats transgenic for HLA-B27 develop arthritis and spondylitis, and this is unaffected by the absence of CD8. It thus appears that classical peptide antigen presentation to CD8+ T cells may not be the primary disease mechanism. However, the association of AS with ERAP1, which strongly influences the MHC class I peptide repertoire, is only found in B27+ patients, and this suggests that peptide binding to B27 is nonetheless important. T e pairs of ERAP1 alleles found in AS patients show diminished peptidase activity, compared with those found in healthy controls. T e B27 heavy chain has an unusual tendency to misfold, a process that may be proinflammatory. Genetic and functional studies in humans have suggested a role for natural killer (NK) cells in AS, possibly through interaction with B27 heavy chain homodimers. SpA-prone B27 rats show defective dendritic cell function and share with AS patients a characteristic "reverse interferon" gene expression signature in antigen-presenting cells.

New bone formation in AS appears to be largely based on enchondral bone formation and occurs only in the periosteal compartment. It correlates with lack of regulation of the Wnt signaling pathway, which controls the differentiation of mesenchymal cells into osteophytes, by the inhibitors DKK-1 and sclerostin. Indirect evidence and data from animal models also implicate bone morphogenic proteins, hedgehog proteins, and prostaglandin E_2. T ere is sharp controversy as to whether vertebral new bone formation in AS is a sequela of inflammation or whether it arises independently of inflammation. T e second hypothesis is based on the observation that syndesmophyte formation is not suppressed by anti-TNF-α therapy that potently suppresses inflammation. TNF-α is also a known inducer of DKK-1, which inhibits bone formation. Recent magnetic resonance imaging (MRI) studies suggest that it is vertebral inflammatory lesions that undergo metaplasia to fat (increased T1-weighted signal) that are the predominant site of subsequent syndesmophytes despite anti-TNF-α therapy, whereas early acute inflammatory lesions resolve. A recent study suggested that the rate of syndesmophyte formation decreases after >4 years of anti-TNF-α therapy.

CLINICAL MANIFESTATIONS

T e symptoms of the disease are usually first noticed in late adolescence or early adulthood; the median age in Western countries is approximately 23 years. In 5% of patients, symptoms begin after age 40. T e initial symptom is usually dull pain, insidious in onset, felt deep in the lower lumbar or gluteal region, accompanied by low-back morning stiffness of up to a few hours' duration that improves with activity and returns following inactivity. Within a few months, the pain has usually become persistent and bilateral. Nocturnal exacerbation of pain often forces the patient to rise and move around.

In some patients, bony tenderness (presumably reflecting enthesitis or osteitis) may accompany back pain or stiffness, whereas in others it may be the predominant complaint. Common sites include the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels. Hip and shoulder ("root" joint) arthritis is considered part of the axial disease. Hip arthritis occurs in 25–35% of patients. Shoulder arthritis is much less common. Severe isolated hip arthritis or bony chest pain may be the presenting complaint, and symptomatic hip disease can dominate the clinical picture. Arthritis of peripheral joints other than the hips and shoulders, usually asymmetric, occurs in up to 30% of patients. Neck pain and stiffness from involvement of the cervical spine are usually relatively late manifestations but are occasionally dominant symptoms. Rare patients, particularly in the older age group, present with predominantly constitutional symptoms.

AS often has a juvenile onset in developing countries. Peripheral arthritis and enthesitis usually predominate, with axial symptoms supervening in late adolescence.

Initially, physical findings mirror the inflammatory process. T e most specific findings involve loss of spinal mobility, with limitation of anterior and lateral flexion and extension of the lumbar spine and of chest expansion. Limitation of motion is usually out of proportion to the degree of bony ankylosis and is thought to possibly reflect muscle spasm secondary to pain and inflammation. Pain in the sacroiliac joints may be elicited either with direct pressure or with stress on the joints. In addition, there is commonly tenderness upon palpation of the posterior spinous processes and other sites of symptomatic bony tenderness.

T e modified Schober test is a useful measure of lumbar spine flexion. T e patient stands erect, with

heels together, and marks are made on the spine at the lumbosacral junction (identified by a horizontal line between the posterosuperior iliac spines) and 10 cm above. T e patient then bends forward maximally with knees fully extended, and the distance between the two marks is measured. T is distance increases by ≥5 cm in the case of normal mobility and by <4 cm in the case of decreased mobility. Chest expansion is measured as the difference between maximal inspiration and maximal forced expiration in the fourth intercostal space in males or just below the breasts in females, with the patient's hands resting on or just behind the head. Normal chest expansion is ≥5 cm. Lateral bending measures the distance the patient's middle finger travels down the leg with maximal lateral bending. Normal is >10 cm.

Limitation or pain with motion of the hips or shoulders is usually present if these joints are involved. It should be emphasized that early in the course of mild cases, symptoms may be subtle and nonspecific, and the physical examination may be unrevealing.

T e course of the disease is extremely variable, ranging from the individual with mild stiffness and normal radiographs to the patient with a totally fused spine and severe bilateral hip arthritis, accompanied by severe peripheral arthritis and extraarticular manifestations. Pain tends to be persistent early in the disease and intermittent later, with alternating exacerbations and quiescent periods. In a typical severe untreated case with progression of the spondylitis to syndesmophyte formation, the patient's posture undergoes characteristic changes, with obliterated lumbar lordosis, buttock atrophy, and accentuated thoracic kyphosis. T ere may be a forward stoop of the neck or flexion contractures at the hips, compensated by flexion at the knees. Disease progression can be estimated clinically from loss of height, limitation of chest expansion and spinal flexion, and occiput-to-wall distance. Occasional individuals are encountered with advanced deformities who report having never had significant symptoms.

T e factors most predictive of radiographic progression (see below) are the presence of existing syndesmophytes, high inflammatory makers, and smoking. In some but not all studies, onset of AS in adolescence and early hip involvement correlate with a worse prognosis. In women, AS tends to progress less frequently to total spinal ankylosis, although there may be an increased prevalence of isolated cervical ankylosis and peripheral arthritis. In industrialized countries, peripheral arthritis (distal to hips and shoulders) occurs in less than one-half of patients with AS, usually as a late manifestation, whereas in developing countries, the prevalence is much higher, with onset typically early in the disease course. Pregnancy has no consistent effect on AS, with symptoms improving, remaining the same, or deteriorating in one-third of pregnant patients, respectively.

T e most serious complication of the spinal disease is spinal fracture, which can occur with even minor trauma to the rigid, osteoporotic spine. T e lower cervical spine is most commonly involved. T ese fractures are often displaced and cause spinal cord injury. A recent survey suggested a >10% lifetime risk of fracture. Occasionally, fracture through a diskovertebral junction and adjacent neural arch, termed pseudoarthrosis, most common in the thoracolumbar spine, can be an unrecognized source of persistent localized pain and/or neurologic dysfunction. Wedging of thoracic vertebrae is common and correlates with accentuated kyphosis.

T e most common extraarticular manifestation is acute anterior uveitis, which occurs in up to 40% of patients and can antedate the spondylitis. Attacks are typically unilateral, causing pain, photophobia, and increased lacrimation. T ese tend to recur, often in the opposite eye. Cataracts and secondary glaucoma are not uncommon sequelae. Up to 60% of patients with AS have inflammation in the colon or ileum. T is is usually asymptomatic, but frank IBD occurs in 5–10% of patients with AS (see "Enteropathic Arthritis," p. 154). About 10% of patients meeting criteria for AS have psoriasis (see "Psoriatic Arthritis," p. 150). Aortic insufficiency, sometimes leading to congestive heart failure, occurs in a small percentage of patients, occasionally early. T ird-degree heart block may occur alone or together with aortic insuf ciency. Subclinical pulmonary lesions and cardiac dysfunction may be relatively common. Cauda equina syndrome and upper pulmonary lobe fibrosis are rare late complications. Retroperitoneal fibrosis is a rare associated condition. Prostatitis has been reported to have an increased prevalence. Amyloidosis is rare.

Several validated measures of disease activity and functional outcome are in widespread use in the study and management of AS, particularly the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), both measures of disease activity; the Bath Ankylosing Spondylitis Functional Index (BASFI), a measure of limitation in activities of daily living; and several measures of radiographic changes. T e Harris hip score, although not specific for AS, can be helpful. Despite persistence of the disease, most patients remain gainfully employed. Some but not all studies of survival in AS have suggested that AS shortens life span, compared with the general population. Mortality attributable to AS is largely the result of spinal trauma, aortic insuf ciency, respiratory failure, amyloid nephropathy, or complications of therapy such as upper gastrointestinal hemorrhage. T e impact of anti-TNF therapy on outcome and mortality is not yet known, except for significantly improved work productivity.

LABORATORY FINDINGS

No laboratory test is diagnostic of AS. In most ethnic groups, HLA-B27 is present in 80–90% of patients. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often, but not always, elevated. Mild anemia may be present. Patients with severe disease may show an elevated alkaline phosphatase level. Elevated serum IgA levels are common. Rheumatoid factor, anti-cyclic citrullinated peptide (CCP), and antinuclear antibodies (ANAs) are largely absent unless caused by a coexistent disease, although ANAs may appear with anti-TNF therapy. Circulating levels of CD8+ T cells tend to be low, and serum matrix metalloproteinase 3 levels correlate with disease activity. Synovial fluid from peripheral joints in AS is nonspecifically inflammatory. In cases with restriction of chest wall motion, decreased vital capacity and increased functional residual capacity are common, but airflow is normal and ventilatory function is usually well maintained.

RADIOGRAPHIC FINDINGS

Radiographically demonstrable sacroiliitis, usually symmetric, is eventually present in AS. T e earliest changes by standard radiography are blurring of the cortical margins of the subchondral bone, followed by erosions and sclerosis. Progression of the erosions leads to "pseudowidening" of the joint space; as fibrous and then bony ankylosis supervene, the joints may become obliterated.

In the lumbar spine, progression of the disease leads to straightening, caused by loss of lordosis, and reactive sclerosis, caused by osteitis of the anterior corners of the vertebral bodies with subsequent erosion, leading to "squaring" or even "barreling" of one or more vertebral bodies. Progressive ossification leads to eventual formation of marginal syndesmophytes, visible on plain films as bony bridges connecting successive vertebral bodies anteriorly and laterally.

Years may elapse before unequivocal sacroiliac abnormalities are evident on plain radiographs, and consequently, MRI is being increasingly used in diagnosing AS. Active sacroiliitis is best visualized by dynamic MRI with fat saturation, either T2-weighed turbo spin-echo sequence or short tau inversion recovery (STIR) with high resolution, or T1-weighted images with contrast enhancement. T ese techniques sensitively identify early intraarticular inflammation, cartilage changes, and underlying bone marrow edema in sacroiliitis **(Fig. 10-1)**. T ey are also highly sensitive for evaluation of acute and chronic spinal changes **(Fig. 10-2)**.

Reduced bone mineral density can be detected by dual-energy x-ray absorptiometry of the femoral neck and the lumbar spine. Use of a lateral projection of the L3 vertebral body can prevent falsely elevated readings related to spinal ossification.

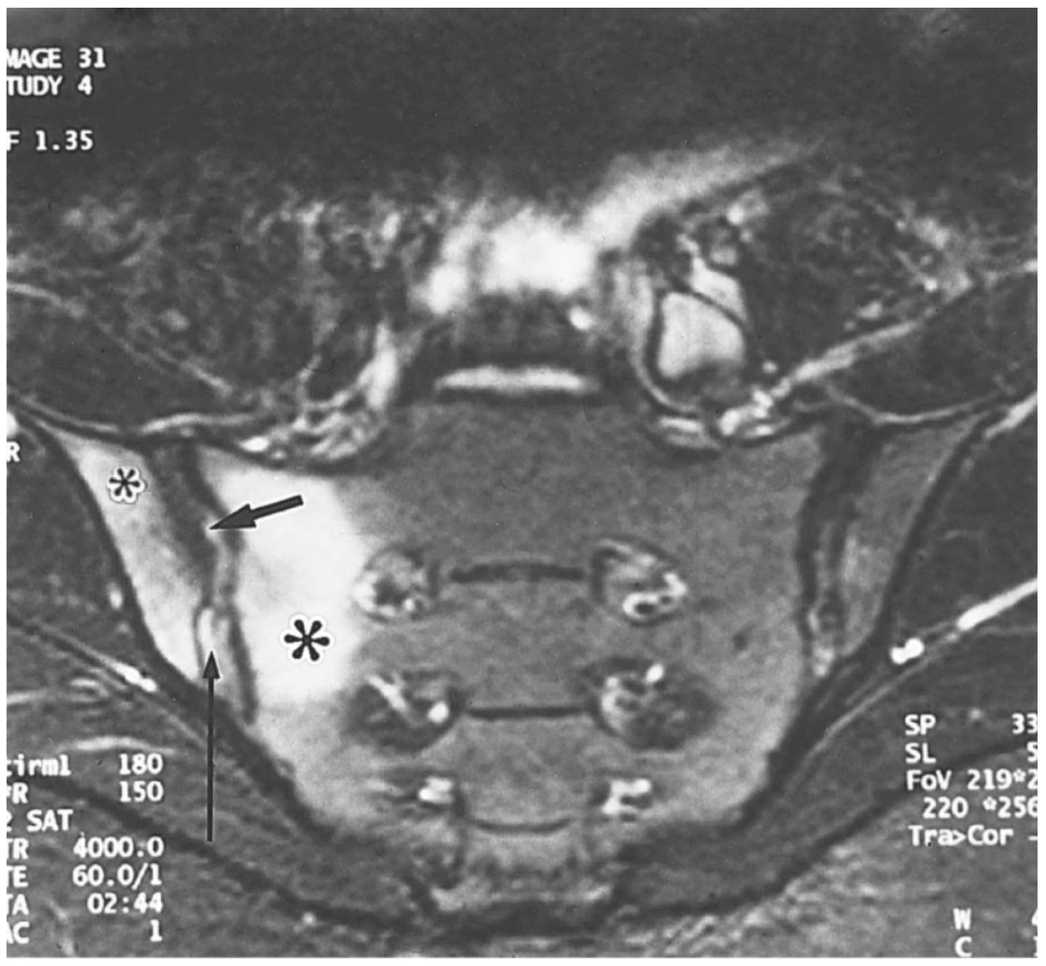


FIGURE 10-1
Early sacroiliitis in a patient with ankylosing spondylitis, indicated by prominent edema in the juxtaarticular bone marrow (asterisks), synovium and joint capsule (thin arrow), and interosseous ligaments (thick arrow) on a short tau inversion recovery (STIR) magnetic resonance image. (From M Bollow et al: Zeitschrift für Rheumatologie 58:61, 1999. Reproduced with permission.)

DIAGNOSIS

It is important to establish the diagnosis of early AS before the development of irreversible deformity. T is goal presents a challenge for several reasons: (1) Back pain is very common, but AS is much less common; (2) an early presumptive diagnosis often relies on clinical grounds requiring considerable expertise; and (3) young individuals with symptoms of AS often do not seek medical care. T e widely used modified New York criteria (1984) are based on the presence of definite radiographic sacroiliitis and are too insensitive in early or mild cases. In 2009, new criteria for axial SpA were proposed by the Assessment of Spondyloarthritis International Society (ASAS)(Table 10-1). T ey are applicable to individuals with ≥3 months of back pain with age of onset <45 years old. Active inflammation of the sacroiliac joints as determined by dynamic MRI is considered equivalent to definite radiographic sacroiliitis (see below).

AS must be differentiated from numerous other causes of low-back pain, some far more common than AS. To qualify as the criterion for inflammatory back pain of axial SpA (Table 10-1), the chronic (≥3 months)

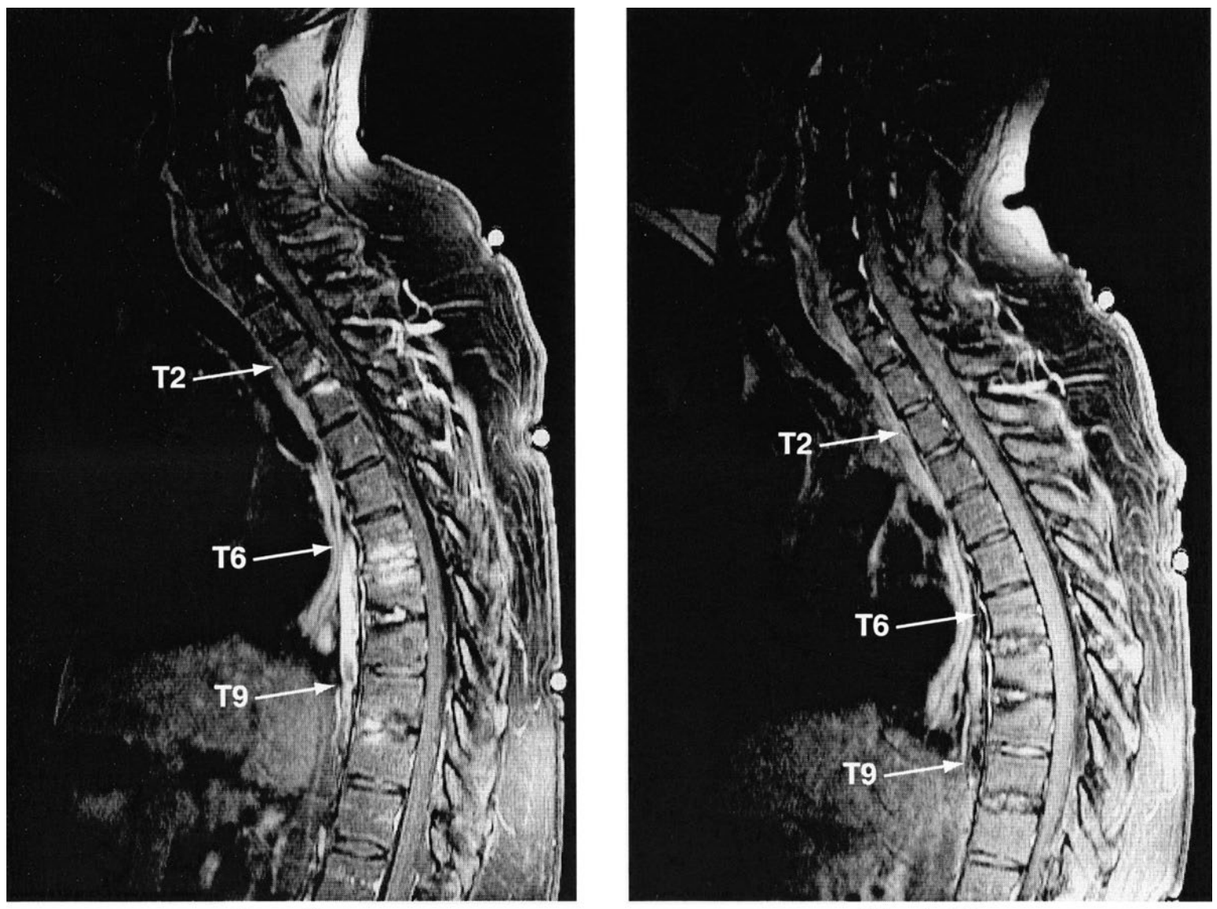


FIGURE 10-2
Spinal inflammation (spondylodiskitis) in a patient with ankylosing spondylitis and its dramatic response to treatment with infliximab. Gadolinium-enhanced T1-weighted magnetic resonance images, with fat saturation, at baseline and after 24 weeks of infliximab therapy. (From J Braun et al: Arthritis Rheum 54:1646, 2006.)

back pain should have four or more of the following characteristic features: (1) age of onset <40 years old; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; and (5) pain at night with improvement upon getting up. Other common features of inflammatory back pain include morning stiffness >30 min, awakening from back pain during only the second half of the night, and alternating buttock pain. In clinical decision-making, all of these features are additive. The most common causes of back pain other than AS are primarily mechanical or degenerative rather than primarily inflammatory and tend not to show clustering of these features.

Less-common metabolic, infectious, and malignant causes of back pain must also be differentiated from AS, including infectious spondylitis, spondylodiskitis, and sacroiliitis, and primary or metastatic tumor. Ochronosis can produce a phenotype that is clinically and radiographically similar to AS. Calcification and ossification of paraspinous ligaments occur in diffuse idiopathic skeletal hyperostosis (DISH), which occurs in the middle-aged and elderly and is usually not symptomatic. Ligamentous calcification gives the appearance of "flowing wax" on the anterior bodies of the vertebrae. Intervertebral disk spaces are preserved, and sacroiliac and apophyseal joints appear normal, helping to differentiate DISH from spondylosis and from AS, respectively.

TREATMENT Ankylosing Spondylitis

All management of AS should include an exercise program designed to maintain posture and range of motion. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of pharmacologic therapy for AS. These agents reduce pain and tenderness and increase mobility in many patients with AS. There is mounting evidence that continuous high-dose NSAID therapy slows radiographic progression, particularly in patients who are at higher risk for progression. However, many patients with AS have continued symptoms despite NSAID therapy and are likely to benefit from anti-TNF-α therapy. Patients with AS treated with infliximab (chimeric human/mouse anti-TNF-α monoclonal antibody), etanercept (soluble p75 TNF-α receptor–IgG fusion protein), adalimumab, or golimumab (human anti-TNF-α monoclonal antibodies, or certolizumab pegol [humanized mouse anti-TNF-α monoclonal antibody]) have shown rapid, profound, and sustained reductions in all clinical and laboratory measures of disease activity. In a good response, there is significant improvement in both objective and subjective indicators of disease activity and function, including morning stiffness, pain, spinal mobility, peripheral joint swelling, CRP, and ESR. MRI studies indicate substantial resolution of bone marrow edema, enthesitis, and joint effusions in the sacroiliac joints, spine, and peripheral joints (Fig. 10-2). Similar results have been obtained in large randomized controlled trials of all four agents and many open-label studies. About one-half of the patients achieve a ≥50% reduction in the BASDAI. The response tends to be stable over time, and partial or full remissions are common. Predictors of the best responses include younger age, shorter disease duration, higher baseline inflammatory markers, and lower baseline functional disability. Nonetheless, some patients with long-standing disease and even spinal ankylosis can obtain significant benefit. Increased bone mineral density is found as early as 24 weeks after onset of therapy. There is evidence that anti-TNF therapy does not prevent syndesmophyte formation, although this may apply mainly during the early years of therapy. A mechanism for this has been proposed based on the observation that TNF-α inhibits new bone formation by upregulating

DKK-1, a negative regulator of the wingless (Wnt) signaling pathway that promotes osteoblast activity. Serum DKK-1 levels are inappropriately low in AS patients and are also suppressed by anti-TNF therapy.

Infliximab is given intravenously, 3–5 mg/kg body weight, and then repeated 2 weeks later, again 6 weeks later, and then at 8-week intervals. Etanercept is given by subcutaneous injection, 50 mg once weekly. Adalimumab is given by subcutaneous injection, 40 mg biweekly. Golimumab is given by subcutaneous injection, 50 or 100 mg every 4 weeks. Certolizumab pegol is given by subcutaneous injection, 400 mg every 4 weeks.

Although these potent immunosuppressive agents have thus far been relatively safe, patients are at increased risk for serious infections, including disseminated tuberculosis. Hypersensitivity infusion or injection site reactions are not uncommon. Cases of anti-TNF-induced psoriasis have been increasingly recognized. Rare cases of systemic lupus erythematosus–related disease have been reported, as have hematologic disorders such as pancytopenia, demyelinating disorders, exacerbation of congestive heart failure, and severe liver disease. T e overall incidence of malignancy does not appear to be increased in AS patients treated with anti-TNF therapy, but isolated cases of hematologic malignancy have occurred shortly after the start of treatment.

Because of the expense, potentially serious side effects, and unknown long-term effects of these agents, their use should be restricted to patients with a definite diagnosis and active disease (BASDAI ≥4 out of 10 and expert opinion) that is inadequately responsive to therapy with at least two different NSAIDs. Before initiation of anti-TNF therapy, all patients should be tested for tuberculin (TB) reactivity, and reactors (≥5 mm on PPD testing or a positive quantiferon test) should be treated with anti-TB agents. Contraindications include active infection or high risk of infection; malignancy or premalignancy; and history of systemic lupus erythematosus, multiple sclerosis, or related autoimmunity. Pregnancy and breast-feeding are relative contraindications. Continuation beyond 12 weeks of therapy requires either a 50% reduction in BASDAI or absolute reduction of ≥2 out of 10, and favorable expert opinion. Switching to a second anti-TNF agent may be effective, especially if there was a response to the first that was lost rather than primary failure. Sulfasalazine, in doses of 2–3 g/d, has been shown to be of modest benefit, primarily for peripheral arthritis. A therapeutic trial of this agent should precede any use of anti-TNF agents in patients with predominantly peripheral arthritis. Methotrexate, although widely used, has not been shown to be of benefit in AS, nor has any therapeutic role for gold or oral glucocorticoids been documented. Potential benefit in AS has been reported for thalidomide, 200 mg/d, perhaps acting through inhibition of TNF-α.

Secukinumab (anti-IL17) was recently approved by the U.S. Food and Drug Administration for the treatment of AS. Ustekinumab (anti-IL-12/23) monoclonal antibody has shown promising ef cacy in clinical trials, but has not yet been approved for use in AS.

T e most common indication for surgery in patients with AS is severe hip joint arthritis, the pain and stiffness of which are usually dramatically relieved by total hip arthroplasty. Rare patients may benefit from surgical correction of extreme flexion deformities of the spine or of atlantoaxial subluxation.

Attacks of uveitis are usually managed effectively with local glucocorticoid administration in conjunction with mydriatic agents, although systemic glucocorticoids, immunosuppressive drugs, or anti-TNF therapy may be required. TNF inhibitors reduce the frequency of attacks of uveitis in patients with AS, although cases of new or recurrent uveitis after use of a TNF inhibitor have been observed, especially with etanercept.

Coexistent cardiac disease may require pacemaker implantation and/or aortic valve replacement. Management of axial osteoporosis is at present similar to that used for primary osteoporosis, since data specific for AS are not available.

REACTIVE ARTHRITIS

Reactive arthritis (ReA) refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. In recent years, the term has been used primarily to refer to SpA following enteric or urogenital infections.

HISTORIC BACKGROUND

T e association of acute arthritis with episodes of diarrhea or urethritis has been recognized for centuries. A large number of cases during World Wars I and II focused attention on the triad of arthritis, urethritis, and conjunctivitis, often with additional mucocutaneous lesions, which became widely known by eponyms that are now of historic interest only.

T e identification of bacterial species capable of triggering the clinical syndrome and the finding that many patients possess the B27 antigen led to the unifying concept of ReA as a clinical syndrome triggered by specific etiologic agents in a genetically susceptible host. A similar spectrum of clinical manifestations can be triggered by enteric infection with any of several Shigella, Salmonella, Yersinia, and Campylobacter species; by genital infection with Chlamydia trachomatis; and by other agents as well. T e triad of arthritis, urethritis, and conjunctivitis represents a small part of the spectrum of the clinical manifestations of ReA and only a minority of patients present with this "classic triad" of symptoms. Although emerging data suggest that asymptomatic Chlamydia trachomatis infections might trigger ReA, for the purposes of this chapter, the use of the term ReA will be restricted to those cases of SpA in which there is at least presumptive

evidence for a related symptomatic antecedent infection. Patients with clinical features of ReA who lack evidence of an antecedent infection will be considered to have undi*ff*erentiated spondyloarthritis, discussed below.

EPIDEMIOLOGY

Initial reports may have overestimated the association of ReA with HLA-B27, since 60–85% of patients who developed ReA triggered by Shigella, Yersinia, or Chlamydia were B27-positive. However, other studies demonstrated a lower prevalence of B27 in ReA triggered by Salmonella, with one study suggesting no association in Campylobacter-induced ReA. Several more recent community-based or common-source epidemic studies demonstrated that the prevalence of B27 in ReA was below 50%. T e most common age range is 18–40 years, but ReA can occur rarely in children and occasionally in older adults.

T e attack rate of postenteric ReA generally ranges from 1% to about 30% depending on the study and causative organism, whereas the attack rate of postchlamydial ReA is about 4–8%. T e gender ratio in ReA following enteric infection is nearly 1:1, whereas venereally acquired ReA occurs mainly in men. T e overall prevalence and incidence of ReA are dif cult to assess because of the lack of validated diagnostic criteria, variable prevalence and arthritogenic potential of the triggering infectious agents, and inconstant genetic susceptibility factors in different populations. In Scandinavia, an annual incidence of 10–28:100,000 has been reported. T e spondyloarthritides were formerly almost unknown in sub-Saharan Africa. However, ReA and other peripheral SpAs have now become the most common rheumatic diseases in Africans in the wake of the AIDS epidemic, without association to B27, which is very rare in these populations. ReA is often the first manifestation of HIV infection and often remits with disease progression. In contrast, Western white patients with HIV and SpA are usually B27-positive, and the arthritis flares as AIDS advances.

PATHOLOGY

Synovial histology is similar to that of other SpAs. Enthesitis shows increased vascularity and macrophage infiltration of fibrocartilage. Microscopic histopathologic evidence of inflammation mimicking IBD has routinely been demonstrated in the colon and ileum of patients with postenteric ReA and less commonly in postvenereal ReA. T e skin lesions of keratoderma blennorrhagica, associated mainly with venereally acquired ReA, are histologically indistinguishable from pustular psoriatic lesions.

ETIOLOGY AND PATHOGENESIS

T e bacteria identified as definitive triggers of ReA include several Salmonella spp., Shigella spp., Yersinia enterocolitica, Yersinia pseudotuberculosis, Campylobacter jejuni, and Chlamydia trachomatis. T ese triggering microbes are gram-negative bacteria with a lipopolysaccharide component to their cell walls. All four Shigella species (Shigella sonnei, Shigella boydii, Shigella *fl*exneri, and Shigella dysenteriae) have been implicated in cases of ReA, with S. *fl*exneri and S. sonnei being the most common. After Salmonella infection, individuals of Caucasian descent may be more likely than those of Asian descent to develop ReA. Children may be less susceptible to ReA caused by Salmonella and Campylobacter. Yersinia species in Europe and Scandinavia may have greater arthritogenic potential than in other parts of the world, and C. trachomatis appears to be a common cause worldwide. T e ocular serovars of C. trachomatis appear to be particularly, perhaps uniquely, arthritogenic.

T ere is also evidence implicating Clostridium di*ff*cile, Campylobacter coli, certain toxigenic Escherichia coli, and possibly Ureaplasma urealyticum and Mycoplasma genitalium as potential triggers of ReA. Chlamydia pneumoniae is another trigger of ReA, albeit far less common than C. trachomatis. T ere have also been numerous isolated reports of acute arthritis preceded by other bacterial, viral, or parasitic infections, and even following intravesicular bacillus Calmette-Guérin (BCG) treatment for bladder cancer.

It has not been determined whether ReA occurs by the same pathogenic mechanism following infection with each of these microorganisms, nor has the mechanism been elucidated in the case of any one of the known bacterial triggers. Most, if not all, of the organisms well established to be triggers share a capacity to attack mucosal surfaces, to invade host cells, and to survive intracellularly. Antigens from Chlamydia, Yersinia, Salmonella, and Shigella have been shown to be present in the synovium and/or synovial fluid leukocytes of patients with ReA for long periods following the acute attack. In ReA triggered by Y. enterocolitica, bacterial lipopolysaccharide (LPS) and heat-shock protein antigens have been found in peripheral blood cells years after the triggering infection. Yersinia DNA and C. trachomatis DNA and RNA have been detected in synovial tissue from ReA patients, suggesting the presence of viable organisms despite uniform failure to culture the organism from these specimens. In C. trachomatis–induced ReA specifically, the bacterial load in synovial tissue of patients with remitting disease is lower than that of active disease, but mRNAs encoding proinflammatory proteins are equal to or higher than those of active disease. T e specificity of these findings is unclear, however, since chromosomal bacterial

DNA and 16S rRNA from a very wide variety of bacteria have also been found in synovium in other rheumatic diseases, albeit less frequently. In several older studies, synovial T cells that specifically responded to antigens of the inciting organism were reported and characterized as predominantly CD4+ with a T_H2 or T regulatory phenotype. More recent work has documented high levels of IL-17 in ReA synovial fluid, but the source has not been identified. HLA-B27 seems to be associated with more severe and chronic forms of the "classic triad" of ReA, but its pathogenic role remains to be determined. HLA-B27 significantly prolongs the intracellular survival of Y. enterocolitica and Salmonella enteritidis in human and mouse cell lines. Prolonged intracellular bacterial survival, promoted by B27, other factors, or both, may permit traf cking of infected leukocytes from the site of primary infection to joints, where an innate and/or adaptive immune response to persistent bacterial antigens may then promote arthritis.

CLINICAL FEATURES

T e clinical manifestations of ReA constitute a spectrum that ranges from an isolated, transient monoarthritis or enthesitis to severe multisystem disease. A careful history will usually elicit evidence of an antecedent infection 1–4 weeks before onset of symptoms of the reactive disease, particularly in postenteric ReA. However, in a sizable minority, no clinical or laboratory evidence of an antecedent infection can be found, particularly in the case of postchlamydial ReA. In cases of presumed venereally acquired reactive disease, there is often a history of a recent new sexual partner, even without laboratory evidence of infection.

Constitutional symptoms are common, including fatigue, malaise, fever, and weight loss. T e musculoskeletal symptoms are usually acute in onset. Arthritis is usually asymmetric and additive, with involvement of new joints occurring over a few days to 1–2 weeks. T e joints of the lower extremities, especially the knee, ankle, and subtalar, metatarsophalangeal, and toe interphalangeal joints, are most commonly involved, but the wrist and fingers can be involved as well. T e arthritis is usually quite painful, and tense joint effusions are not uncommon, especially in the knee. Dactylitis, or "sausage digit," a diffuse swelling of a solitary finger or toe, is a distinctive feature of ReA and other peripheral spondyloarthritides but can be seen in polyarticular gout and sarcoidosis. Tendinitis and fasciitis are particularly characteristic lesions, producing pain at multiple insertion sites (entheses), especially the Achilles insertion, the plantar fascia, and sites along the axial skeleton. Spinal, low-back, and buttock pain are quite common and may be caused by insertional inflammation, muscle spasm, acute sacroiliitis, or, presumably, arthritis in intervertebral joints.

Urogenital lesions may occur throughout the course of the disease. In males, urethritis may be marked or relatively asymptomatic and may be either an accompaniment of the triggering infection or a result of the reactive phase of the disease; interestingly, it occurs in both postvenereal and postenteric ReA. Prostatitis is also common. Similarly, in females, cervicitis or salpingitis may be caused either by the infectious trigger or by the sterile reactive process.

Ocular disease is common, ranging from transient, asymptomatic conjunctivitis to an aggressive anterior uveitis that occasionally proves refractory to treatment and may result in blindness.

Mucocutaneous lesions are frequent. Oral ulcers tend to be superficial, transient, and often asymptomatic. T e characteristic skin lesions, keratoderma blennorrhagica, consist of vesicles and/or pustules that become hyperkeratotic, ultimately forming a crust before disappearing. T ey are most common on the palms and soles but may occur elsewhere as well. In patients with HIV infection, these lesions are often extremely severe and extensive, sometimes dominating the clinical picture. Lesions may occur on the glans penis, termed circinate balanitis; these consist of vesicles that quickly rupture to form painless superficial erosions, which in circumcised individuals can form crusts similar to those of keratoderma blennorrhagica. Nail changes are common and consist of onycholysis, distal yellowish discoloration, and/or heaped-up hyperkeratosis.

Less-frequent or rare manifestations of ReA include cardiac conduction defects, aortic insuf ciency, central or peripheral nervous system lesions, and pleuropulmonary infiltrates.

Arthritis typically persists for 3–5 months, but more chronic courses do occur. Chronic joint symptoms persist in about 15% of patients and in up to 60% of patients in hospital-based series, but these tend to be less severe than in the acute stage. Recurrences of the acute syndrome are also common. Work disability or forced change in occupation is common in those with persistent joint symptoms. Chronic heel pain is often particularly distressing. Low-back pain, sacroiliitis, and frank AS are also common sequelae. In most studies, HLA-B27–positive patients have shown a worse outcome than B27-negative patients. Patients with Yersinia- or Salmonella-induced arthritis have less chronic disease than those whose initial episode follows epidemic shigellosis.

LABORATORY AND RADIOGRAPHIC FINDINGS

T e ESR and acute-phase reactants are usually elevated during the acute phase of the disease, often markedly so. Mild anemia may be present. Synovial fluid is nonspecifically inflammatory. In most ethnic groups,

30–50% of the patients are B27-positive. T e triggering infection usually does not persist at the site of primary mucosal infection through the time of onset of the reactive disease, but it may be possible to culture the organism, e.g., in the case of Yersinia- or Chlamydia-induced disease. Serologic evidence of exposure to one of the causative organisms with elevation of antibodies is nonspecific and is of questionable utility. Polymerase chain reaction (PCR) for chlamydial DNA in first-voided urine specimens may have high sensitivity in the acute stage but is less useful with chronic disease.

In early or mild disease, radiographic changes may be absent or confined to juxtaarticular osteoporosis. With long-standing persistent disease, radiographic features share those of psoriatic arthritis; marginal erosions and loss of joint space can be seen in affected joints. Periostitis with reactive new bone formation is characteristic, as in all the SpAs. Spurs at the insertion of the plantar fascia are common.

Sacroiliitis and spondylitis may be seen as late sequelae. Sacroiliitis is more commonly asymmetric than in AS, and spondylitis, rather than ascending symmetrically, can begin anywhere along the lumbar spine. T e syndesmophytes are described as nonmarginal; they are coarse, asymmetric, and "comma"-shaped, arising from the middle of a vertebral body, a pattern less commonly seen in primary AS. Progression to spinal fusion is uncommon.

DIAGNOSIS

ReA is a clinical diagnosis with no definitively diagnostic laboratory test or radiographic finding. T e diagnosis should be entertained in any patient with an acute inflammatory, asymmetric, additive arthritis or tendinitis. T e evaluation should include questioning regarding possible triggering events such as an episode of diarrhea or dysuria. On physical examination, attention must be paid to the distribution of the joint and tendon involvement and to possible sites of extraarticular involvement, such as the eyes, mucous membranes, skin, nails, and genitalia. Synovial fluid analysis may be helpful in excluding septic or crystal-induced arthritis. Culture, serology, or molecular methods may help to identify a triggering infection, but they cannot be relied upon.

Although typing for B27 has low negative predictive value in ReA, it may have prognostic significance in terms of severity, chronicity, and the propensity for spondylitis and uveitis. Furthermore, if positive, it can be helpful diagnostically in atypical cases. HIV testing is often indicated and may be necessary in order to select appropriate therapy.

It is important to differentiate ReA from disseminated gonococcal disease, both of which can be venereally acquired and associated with urethritis. Unlike ReA, gonococcal arthritis and tenosynovitis tend to involve both upper and lower extremities equally, spare the axial skeleton, and be associated with characteristic vesicular skin lesions. A positive gonococcal culture from the urethra or cervix does not exclude a diagnosis of ReA; however, culturing gonococci from blood, skin lesion, or synovium establishes the diagnosis of disseminated gonococcal disease. PCR assay for Neisseria gonorrhoeae and C. trachomatis may be helpful. Occasionally, only a therapeutic trial of antibiotics can distinguish the two.

ReA shares many features in common with psoriatic arthropathy. However, psoriatic arthritis is usually gradual in onset; the arthritis tends to affect primarily the upper extremities; there is less associated periarthritis; and there are usually no associated mouth ulcers, urethritis, or bowel symptoms.

TREATMENT Reactive Arthritis

Most patients with ReA benefit to some degree from high-dose NSAIDs, although acute symptoms are rarely completely ameliorated, and some patients fail to respond at all. Indomethacin, 75–150 mg/d in divided doses, is the initial treatment of choice, but other NSAIDs may be tried.

Prompt, appropriate antibiotic treatment of acute chlamydial urethritis or enteric infection may prevent the emergence of ReA, but is not universally successful. Data regarding the potential benefit of antibiotic therapy that is initiated after onset of arthritis are conflicting, but several trials suggest no benefit. One long-term follow-up study suggested that although antibiotic therapy had no effect on the acute episode of ReA, it helped prevent subsequent chronic SpA. Another such study failed to demonstrate any long-term benefit. A promising recent double-blind placebo-controlled study assessing combination antibiotics showed that a majority of patients with chronic ReA due to Chlamydia benefited significantly from a 6-month course of rifampin 300 mg daily plus azithromycin 500 mg daily for 5 days, then twice weekly, or 6 months of rifampin 300 mg daily plus doxycycline 100 mg twice daily. T e possibility remains that acute Chlamydia-induced ReA might respond more favorably to antibiotic therapy than the postenteric variety.

Multicenter trials have suggested that sulfasalazine, up to 3 g/d in divided doses, may be beneficial to patients with persistent ReA.[1] Patients with persistent disease may respond to azathioprine, 1–2 mg/kg per day, or to methotrexate, up to 20 mg per week; however, these therapeutic regimens have never formally been studied. Although no controlled trials of anti-TNF-α in ReA have been reported, anecdotal evidence supports the use of these agents in severe chronic cases, although lack of response has also been observed. (Azathioprine, methotrexate, sulfasalazine, pamidronate, and thalidomide have not been approved for this purpose by the U.S. Food and Drug Administration at the time of publication.)

Tendinitis and other enthesitic lesions may benefit from intralesional glucocorticoids. Uveitis may require aggressive treatment to prevent serious sequelae (see above). Skin lesions ordinarily require only symptomatic topical treatment. In patients with HIV infection and ReA, many of whom have severe skin lesions, the skin lesions in particular respond to antiretroviral therapy. Cardiac complications are managed conventionally; management of neurologic complications is symptomatic.

Comprehensive management includes counseling of patients in the avoidance of sexually transmitted disease and exposure to enteropathogens, as well as appropriate use of physical therapy, vocational counseling, and continued surveillance for long-term complications such as AS. Patients with a history of ReA are at increased risk for recurrent attacks following repeated exposures.

PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) refers to an inflammatory musculoskeletal disease that has both autoimmune and autoinflammatory features characteristically occurring in individuals with psoriasis.

HISTORIC BACKGROUND

T e association between arthritis and psoriasis was noted in the nineteenth century. In the 1960s, on the basis of epidemiologic and clinical studies, it became clear that unlike RA, the arthritis associated with psoriasis was usually seronegative, often involved the distal interphalangeal (DIP) joints of the fingers and the spine and sacroiliac joints, had distinctive radiographic features, and showed considerable familial aggregation. In the 1970s, PsA was included in the broader category of the spondyloarthritides because of features similar to those of AS and ReA.

EPIDEMIOLOGY

Estimates of the prevalence of PsA among individuals with psoriasis range from 5 to 42%. T e prevalence of PsA appears to be increasing in parallel with disease awareness; recent data using screening tools suggest that 20% or more of patients with psoriasis have undiagnosed PsA. T e duration and severity of psoriasis increase one's likelihood of developing PsA. In white populations, psoriasis is estimated to have a prevalence of 1–3%. Psoriasis and PsA are less common in other races in the absence of HIV infection, and the prevalence of PsA in individuals with psoriasis may be less common. First-degree relatives of PsA patients have an elevated risk for psoriasis, for PsA itself, and for other forms of SpA. Of patients with psoriasis, up to 30% have an affected first-degree relative. In monozygotic twins, the reported concordance for psoriasis varies from 35 to 72%, and for PsA from 10 to 30%. A variety of HLA associations have been found. T e HLA-Cw*0602 gene is directly associated with psoriasis, particularly familial juvenile-onset (type I) psoriasis. HLA-B27 is associated with psoriatic spondylitis (see below). HLA-DR7, -DQ3, and -B57 are associated with PsA because of linkage disequilibrium with Cw6. Other associations with PsA include HLA-B13, -B37, -B38, -B39, -C12, and -DR4. A recent genome-wide scan found association of both psoriasis and PsA with a polymorphism at the HCP5 locus closely linked to HLA-B, and also to IL-23R, IL-12B (chromosome 5q31), IL-13, and several other chromosomal regions. Certain genetic loci are associated with PsA but not psoriasis, e.g., RUNX3 and IL-13.

PATHOLOGY

T e inflamed synovium in PsA resembles that of RA, although with somewhat less hyperplasia and cellularity than in RA. As noted with AS above, the synovial vascular pattern in PsA is generally greater and more tortuous than in RA, independent of disease duration. Some studies have indicated a higher tendency to synovial fibrosis in PsA. Unlike RA, PsA shows prominent enthesitis, with histology similar to that of the other spondyloarthritides.

PATHOGENESIS

PsA is almost certainly immune-mediated and probably shares pathogenic mechanisms with psoriasis. PsA synovium is characterized by lining layer hyperplasia; diffuse infiltration with T cells, B cells, macrophages, and NK receptor–expressing cells, with upregulation of leukocyte homing receptors; and neutrophil proliferation with angiogenesis. Clonally expanded T cell subpopulations are frequent and have been demonstrated both in the synovium and the skin. Plasmacytoid dendritic cells are thought to play a key role in psoriasis, and there is some evidence for their participation in PsA. T ere is abundant synovial overexpression of proinflammatory cytokines, and synovial tissue staining has identified an overexpression of monocyte-derived cytokines, such as myeloid-related protein (S100A8/A9). Interferon γ, TNF-α, and IL-1β, -2, -6, -8, -10, -12, -13, and -15 are found in PsA synovium or synovial fluid. T_H17-derived cytokines are important in PsA, given the genetic association with genes in the IL-12/IL-23 axis and the therapeutic response to an antibody to the shared IL-12/23 p40 subunit (see below). T_H17 cells have been identified from the dermal extracts of psoriatic lesions and the synovial fluid

of PsA patients. T e majority of these CD4+ IL-17+ T cells are of memory phenotype (CD4RO[+]CD45RA[–] CD11a[+]). Consistent with the extensive bone remodeling in PsA, patients with PsA have been found to have a marked increase in osteoclastic precursors in peripheral blood and upregulation of receptor activator of nuclear factor κβ ligand (RANKL) in the synovial lining layer. Increased serum levels of TNF-α, RANKL, leptin, and omentin positively correlate with these osteoclastic precursors.

CLINICAL FEATURES

In 60–70% of cases, psoriasis precedes joint disease. In 15–20% of cases, the two manifestations appear within 1 year of each other. In about 15–20% of cases, the arthritis precedes the onset of psoriasis and can present a diagnostic challenge. T e frequency in men and women is almost equal, although the frequency of disease patterns differs somewhat in the two sexes. T e disease can begin in childhood or late in life but typically begins in the fourth or fifth decade, at an average age of 37 years.

T e spectrum of arthropathy associated with psoriasis is quite broad. Many classification schemes have been proposed. In the original scheme of Wright and Moll, five patterns are described: (1) arthritis of the DIP joints; (2) asymmetric oligoarthritis; (3) symmetric polyarthritis similar to RA; (4) axial involvement (spine and sacroiliac joints); and (5) arthritis mutilans, a highly destructive form of disease. T ese patterns frequently coexist, and the pattern that persists chronically often differs from that of the initial presentation. A simpler scheme in recent use contains three patterns: oligoarthritis, polyarthritis, and axial arthritis.

Nail changes in the fingers or toes occur in up to 90% of patients with PsA, compared with 40% of psoriatic patients without arthritis, and pustular psoriasis is said to be associated with more severe arthritis. Several articular features distinguish PsA from other joint disorders; such hallmark features include dactylitis and enthesitis. Dactylitis occurs in >30%; enthesitis and tenosynovitis are also common and are probably present in most patients, although often not appreciated on physical examination. Shortening of digits because of underlying osteolysis is particularly characteristic of PsA **(Fig. 10-3)**, and there is a much greater tendency than in RA for both fibrous and bony ankylosis of small joints. Rapid ankylosis of one or more proximal interphalangeal (PIP) joints early in the course of disease is not uncommon. Back and neck pain and stiffness are also common in PsA.

Arthropathy confined to the DIP joints occurs in about 5% of cases. Accompanying nail changes in the

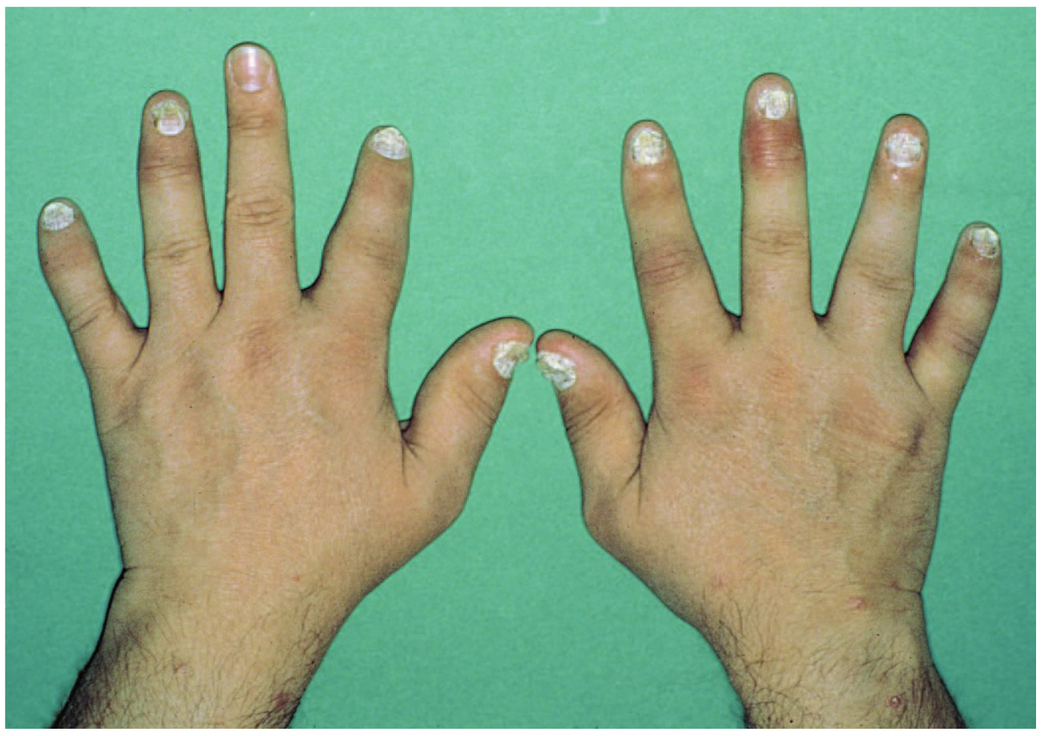


FIGURE 10-3

Characteristic lesions of psoriatic arthritis. Inflammation is prominent in the distal interphalangeal joints (left 5th, 4th, 2nd; right 2nd, 3rd, and 5th) and proximal interphalangeal joints (left 2nd, right 2nd, 4th, and 5th). There is dactylitis in the left 2nd finger and thumb, with pronounced telescoping of the left 2nd finger. Nail dystrophy (hyperkeratosis and onycholysis) affects each of the fingers except the left 3rd finger, the only finger without arthritis. (Courtesy of Donald Raddatz, MD; with permission.)

affected digits are almost always present. T ese joints are also often affected in the other patterns of PsA. Approximately 30% of patients have asymmetric oligoarthritis. T is pattern commonly involves a knee or another large joint with a few small joints in the fingers or toes, often with dactylitis. Symmetric polyarthritis occurs in about 40% of PsA patients at presentation. It may be indistinguishable from RA in terms of the joints involved, but other features characteristic of PsA are usually also present. Almost any peripheral joint can be involved. Axial arthropathy without peripheral involvement is found in about 5% of PsA patients. It may be clinically indistinguishable from idiopathic AS, although more neck involvement and less thoracolumbar spinal involvement are characteristic, and nail changes are not found in idiopathic AS. A small percentage of PsA patients have arthritis mutilans, in which there can be widespread shortening of digits ("telescoping"), sometimes coexisting with ankylosis and contractures in other digits.

Six patterns of nail involvement are identified: pitting, horizontal ridging, onycholysis, yellowish discoloration of the nail margins, dystrophic hyperkeratosis, and combinations of these findings. Other extraarticular manifestations of the spondyloarthritides are common. Eye involvement, either conjunctivitis or uveitis, is reported in 7–33% of PsA patients. Unlike the uveitis associated with AS, the uveitis in PsA is more often bilateral, chronic, and/or posterior. Aortic valve insuf - ciency has been found in <4% of patients, usually after long-standing disease.

Widely varying estimates of clinical outcome have been reported in PsA. At its worst, severe PsA with arthritis mutilans is potentially at least as crippling and ultimately fatal as severe RA. Unlike RA, however, many patients with PsA experience temporary remissions. Overall, erosive disease develops in the majority of patients, progressive disease with deformity and disability is common, and in some large published series, mortality was found to be significantly increased compared with the general population. T ere appears to be a greater incidence of cardiovascular death in psoriatic disease.

T e psoriasis and associated arthropathy seen with HIV infection both tend to be severe and can occur in populations with very little psoriasis in noninfected individuals. Severe enthesopathy, dactylitis, and rapidly progressive joint destruction are seen, but axial involvement is very rare. T is condition is prevented by or responds well to antiretroviral therapy.

LABORATORY AND RADIOGRAPHIC FINDINGS

T ere are no laboratory tests diagnostic of PsA. ESR and CRP are often elevated. A small percentage of patients may have low titers of rheumatoid factor or antinuclear antibodies. About 10% of patients have anti-CCP antibodies. Uric acid may be elevated in the presence of extensive psoriasis. HLA-B27 is found in 50–70% of patients with axial disease, but in ≤20% of patients with only peripheral joint involvement.

T e peripheral and axial arthropathies in PsA show a number of radiographic features that distinguish them from RA and AS, respectively. Characteristics of peripheral PsA include DIP involvement, including the classic "pencil-in-cup" deformity; marginal erosions with adjacent bony proliferation ("whiskering"); small-joint ankylosis; osteolysis of phalangeal and metacarpal bone, with telescoping of digits; and periostitis and proliferative new bone at sites of enthesitis. Characteristics of axial PsA include asymmetric sacroiliitis. When compared with idiopathic AS, axial PsA manifests less zygapophyseal joint arthritis; nonmarginal, bulky, "comma"-shaped syndesmophytes that tend to be fewer and less symmetric and delicate than the marginal syndesmophytes of AS; fluffy hyperperiostosis on anterior vertebral bodies; severe cervical spine involvement, with a tendency to atlantoaxial subluxation but relative sparing of the thoracolumbar spine; and paravertebral ossification. Ultrasound and MRI both readily demonstrate enthesitis and tendon sheath effusions that can be dif cult to assess on physical examination. A recent MRI study of 68 PsA patients found sacroiliitis in 35%, unrelated to B27 but correlated with restricted spinal movement.

DIAGNOSIS

Classification criteria for PsA were published in 2006 (Classification of Psoriatic Arthritis [CASPAR] criteria) that have been widely accepted **(Table 10-2)**. T e sensitivity and specificity of these criteria exceed 90%, and they are useful for early diagnosis. T e criteria are based on the history, presence of psoriasis, characteristic peripheral or spinal joint symptoms, signs, and imaging. Diagnosis can be challenging when the arthritis precedes psoriasis, the psoriasis is undiagnosed or obscure, or the joint involvement closely resembles another form of arthritis. A high index of suspicion is needed in any patient with an undiagnosed inflammatory arthropathy. T e history should include inquiry about psoriasis in the patient and family members. Patients should be asked to disrobe for the physical examination, and psoriasiform lesions should be sought in the scalp, ears, umbilicus, and gluteal folds in addition to more accessible sites; the finger and toe nails should also be carefully examined. Axial symptoms or signs, dactylitis, enthesitis, ankylosis, the pattern of joint involvement, and characteristic radiographic changes can be helpful clues. T e differential diagnosis includes all other forms of arthritis, which can occur coincidentally in individuals with psoriasis. T e differential diagnosis of isolated DIP involvement is short. Osteoarthritis (Heberden's nodes) is usually not inflammatory; gout involving more than one DIP joint often involves other sites and may be accompanied by tophi;

TABLE 10-2

THE CASPAR (CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS) CRITERIA[a]

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from any of the following f ve categories:

1. Evidence of current psoriasis,[b,c] a personal history of psoriasis, or a family history of psoriasis[d]
2. Typical psoriatic nail dystrophy[e] observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis[f] or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation[g] in the hand or foot

[a]Specificity of 99% and sensitivity of 91%.
[b]Current psoriasis is assigned 2 points; all other features are assigned 1 point.
[c]Psoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.
[d]History of psoriasis in a first- or second-degree relative.
[e]Onycholysis, pitting, or hyperkeratosis.
[f]Swelling of an entire digit.
[g]Ill-defined ossification near joint margins, excluding osteophyte formation.
Source: From W Taylor et al: Arthritis Rheum, 54:2665, 2006.

the very rare entity multicentric reticulohistiocytosis involves other joints and has characteristic small pearly periungual skin nodules; and the uncommon entity inflammatory osteoarthritis, like the others, lacks the nail changes of PsA. Radiography can be helpful in all of these cases and in distinguishing between psoriatic spondylitis and idiopathic AS. A history of trauma to an affected joint preceding the onset of arthritis is said to occur more frequently in PsA than in other types of arthritis, perhaps reflecting the Koebner phenomenon in which psoriatic skin lesions can arise at sites of the skin trauma.

TREATMENT Psoriatic Arthritis

Ideally, coordinated therapy is directed at both the skin and joints in PsA. As described above for AS, use of the anti-TNF-α agents has revolutionized the treatment of PsA. Prompt and dramatic resolution of both arthritis and skin lesions has been observed in large, randomized controlled trials of etanercept, infliximab, adalimumab, and golimumab. Many of the responding patients had long-standing disease that was resistant to all previous therapy, as well as extensive skin disease. T e clinical response is often more dramatic than in RA, and delay of disease progression has been demonstrated radiographically. T e potential additive effect of methotrexate to anti-TNF-α agents in PsA remains uncertain. As noted above, anti-TNF therapy, paradoxically, has been reported to trigger exacerbation or de novo appearance of psoriasis, typically the palmoplantar pustular variety. In some cases, the therapy can nevertheless be continued.

Ustekinumab, a monoclonal antibody to the shared IL-23/IL-12p40 subunit, is an ef cacious treatment for psoriasis and PsA and has received approval by the U.S. Food and Drug Administration for both indications. Another newer drug that has shown ef cacy for both psoriasis and PsA is the anti-IL-17 pathway agent, secukinumab. T e oral phosphodiesterase-4 inhibitor, apremilast is used in the treatment of plaque psoriasis and is under active investigation in PsA. Data on the oral Jak inhibitor, tofacitinib, has been very limited but promising.

Other treatment for PsA has been based on drugs that have efficacy in RA and/or in psoriasis. Until recently, controlled clinical trial data on methotrexate in doses of 15–25 mg/week and sulfasalazine (usually given in doses of 2–3 g/d) suggesting clinical ef cacy have been somewhat limited, but neither regimen effectively halts progression of erosive joint disease. A recent double-blind trial assessing methotrexate 15 mg weekly in PsA demonstrated no benefit to the joint-based inflammation, but improvement was seen in patient and assessor global scores and skin scores. Other agents with ef cacy in psoriasis reported to benefit PsA are cyclosporine, retinoic acid derivatives, and psoralens plus ultraviolet A light (PUVA). T ere is controversy regarding the ef cacy in PsA of gold and antimalarials, which have been widely used in RA. T e pyrimidine synthetase inhibitor leflunomide has been shown in a randomized controlled trial to be beneficial in both psoriasis and PsA.

All of these treatments require careful monitoring. Immunosuppressive therapy may be used cautiously in HIV-associated PsA if the HIV infection is well controlled.

UNDIFFERENTIATED AND JUVENILE-ONSET SPONDYLOARTHRITIS

Many patients, usually young adults, present with some features of one or more of the spondyloarthritides discussed above. Until recently, these patients were said to have undi*ff*erentiated spondylo- arthritis, or simply spondyloarthritis, as defined by the 1991 European Spondyloarthropathy Study Group criteria. For example, a patient may present with inflammatory synovitis of one knee, Achilles tendinitis, and dactylitis of one digit. Some of these patients may have ReA in which the triggering infection remains clinically silent. In some other cases, the patient subsequently develops IBD or psoriasis, or the process eventually meets criteria for AS. T is diagnosis of undifferentiated SpA was also commonly applied to patients with inflammatory back pain, who did meet modified New York criteria for AS. Most of these would now be classified under the new category of axial SpA (Table 10-1).

Comparable to the classification criteria for axial symptoms, the ASAS has recently formulated criteria for peripheral SpA. T is is intended to exclude patients with axial symptoms and thus to divide the universe of patients with SpA into axial and exclusively peripheral subsets. T ese criteria are shown in **Table 10-3**.

Approximately one-half of the patients with undifferentiated SpA are HLA-B27-positive, and thus the absence of B27 is not useful in establishing or excluding the diagnosis. In familial cases, which are much more frequently B27-positive, there is often eventual progression to classical AS.

In juvenile-onset SpA, which begins between ages 7 and 16, most commonly in boys (60–80%), an asymmetric, predominantly lower-extremity oligoarthritis and enthesitis without extraarticular features is the typical mode of presentation. T e prevalence of B27 in this condition, which has been termed the seronegative enthesopathy and arthropathy (SEA) syndrome, is approximately 80%. Many, but not all, of these patients go on to develop AS in late adolescence or adulthood.

Management of undifferentiated SpA is similar to that of the other spondyloarthritides. Response to anti-TNF-α therapy has been documented, and this therapy is indicated in severe, persistent cases not responsive to other treatment.

TABLE 10-3

ASAS CRITERIA FOR PERIPHERAL SPONDYLOARTHRITIS[a]

ARTHRITIS[b]	OR PLUS	ENTHESITIS
One or more of the following: • Uveitis • Psoriasis • Crohn's disease or ulcerative colitis OR two or more of the following: • Arthritis • Enthesitis • Dactylitis • Inflammatory back pain ever • Family history for SpA		

[a]Sensitivity 79.5%, specificity 83.3%
[b]Peripheral arthritis, usually predominantly lower limb and/or asymmetric.
Source: M Rudawaleit et al: Ann Rheum Dis 70:25, 2011.

Current pediatric textbooks and journals should be consulted for information on management of juvenile-onset SpA.

ENTEROPATHIC ARTHRITIS

HISTORIC BACKGROUND

A relationship between arthritis and IBD was observed in the 1930s. The relationship was further defined by the epidemiologic studies in the 1950s and 1960s and included in the concept of the spondylo arthritides in the 1970s.

EPIDEMIOLOGY

Both of the common forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD), are associated with SpA. UC and CD both have an estimated prevalence of 0.05–0.1%, and the incidence of each is thought to have increased in recent decades. AS and peripheral arthritis are both associated with UC and CD. Wide variations have been reported in the estimated frequencies of these associations. In recent series, AS was diagnosed in 1–10%, and peripheral arthritis in 10–50% of patients with IBD. Inflammatory back pain and enthesopathy are common, and many patients have sacroiliitis on imaging studies.

The prevalence of UC or CD in patients with AS is thought to be 5–10%. However, investigation of unselected SpA patients by ileocolonoscopy has revealed that from one-third to two-thirds of patients with AS have subclinical intestinal inflammation that is evident either macroscopically or histologically. These lesions have also been found in patients with undifferentiated SpA or ReA (both enterically and urogenitally acquired).

Both UC and CD have a tendency to familial aggregation, more so for CD. HLA associations have been weak and inconsistent. HLA-B27 is found in up to 70% of patients with IBD and AS, but in ≤15% of patients with IBD and peripheral arthritis or IBD alone. Three alleles of the NOD2/CARD15 gene on chromosome 16 have been found in approximately one-half of patients with CD. These alleles are not associated with the spondyloarthritides per se. However, they are found significantly more often in (1) CD patients with sacroiliitis than in those without sacroiliitis, and (2) SpA patients with chronic inflammatory gut lesions than in those with normal gut histology. These associations are independent of HLA-B27. In addition to NOD2, over 100 other genes have been found to be associated with CD, UC, or both. Around 20 of these are also associated with AS.

PATHOLOGY

Available data for IBD-associated peripheral arthritis suggest a synovial histology similar to other spondyloarthritides. Association with arthropathy does not affect the gut histology of UC or CD. The subclinical inflammatory lesions in the colon and distal ileum associated with SpA have been classified as either acute or chronic. The former resemble acute bacterial enteritis, with largely intact architecture and neutrophilic infiltration in the lamina propria. The latter resemble the lesions of CD, with distortion of villi and crypts, aphthoid ulceration, and mononuclear cell infiltration in the lamina propria.

PATHOGENESIS

Both IBD and SpA are immune-mediated, but the specific pathogenic mechanisms are poorly understood, and the connection between the two is obscure. The shared genetics evidently reflects shared pathogenic mechanisms. A number of rodent models showing various immune perturbations manifest both IBD and arthritis. Several lines of evidence indicate trafficking of leukocytes between the gut and the joint. Mucosal leukocytes from IBD patients have been shown to bind avidly to synovial vasculature through several different adhesion molecules. Macrophages expressing CD163 are prominent in the inflammatory lesions of both gut and synovium in the spondyloarthritides.

CLINICAL FEATURES

AS associated with IBD is clinically indistinguishable from idiopathic AS. It runs a course independent of the bowel disease, and in some patients, it precedes the onset of IBD, sometimes by many years. Peripheral

arthritis may also begin before onset of overt bowel disease. T e spectrum of peripheral arthritis includes acute self-limited attacks of oligoarthritis that often coincide with relapses of IBD, and more chronic and symmetric polyarticular arthritis that runs a course independent of IBD activity. T e patterns of joint involvement are similar in UC and CD. In general, erosions and deformities are infrequent in IBD-associated peripheral arthritis, and joint surgery is infrequently required. Isolated destructive hip arthritis is a rare complication of CD, apparently distinct from osteonecrosis and septic arthritis. Dactylitis and enthesopathy are occasionally found. In addition to the □20% of IBD patients with SpA, a comparable percentage have arthralgias or fibromyalgia symptoms.

Other extraintestinal manifestations of IBD are seen in addition to arthropathy, including uveitis, pyoderma gangrenosum, erythema nodosum, and finger clubbing, all somewhat more commonly in CD than UC. T e uveitis shares the features described above for PsA-associated uveitis.

LABORATORY AND RADIOGRAPHIC FINDINGS

Laboratory findings reflect the inflammatory and metabolic manifestations of IBD. Joint fluid is usually at least mildly inflammatory. Of patients with AS and IBD, 30–70% carry the HLA-B27 gene, compared with >85% of patients with AS alone and 50–70% of those with AS and psoriasis. Hence, definite or probable AS in a B27-negative individual in the absence of psoriasis should prompt a search for occult IBD. Radiographic changes in the axial skeleton are the same as in uncomplicated AS. Erosions are uncommon in peripheral arthritis but may occur, particularly in the metatarsophalangeal joints. Isolated destructive hip disease has been described.

DIAGNOSIS

Diarrhea and arthritis are both common conditions that can coexist for a variety of reasons. When etiopathogenically related, ReA and IBD-associated arthritis are the most common causes. Rare causes include celiac disease, blind loop syndromes, and Whipple's disease. In most cases, diagnosis depends on investigation of the bowel disease.

TREATMENT Enteropathic Arthritis

Treatment of CD has been improved by therapy with anti-TNF agents. Infliximab, adalimumab, and certolizumab pegol are effective for induction and maintenance of clinical remission in CD, and infliximab has been shown to be effective in fistulizing CD. IBD-associated arthritis also responds to these agents. Other treatment for IBD, including sulfasalazine and related drugs, systemic glucocorticoids, and immunosuppressive drugs, is also usually of benefit for associated peripheral arthritis. NSAIDs are generally helpful and well tolerated, but they can precipitate flares of IBD. As noted above for psoriasis, rare cases of IBD, either CD or UC, have apparently been precipitated by anti-TNF therapy, usually etanercept, given for any of several rheumatic diseases.

SAPHO SYNDROME

T e syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is characterized by a variety of skin and musculoskeletal manifestations. Dermatologic manifestations include palmoplantar pustulosis, acne conglobata, acne fulminans, and hidradenitis suppurativa. T e main musculoskeletal findings are sternoclavicular and spinal hyperostosis, chronic recurrent foci of sterile osteomyelitis, and axial or peripheral arthritis. Cases with one or a few manifestations are probably the rule. T e ESR is usually elevated, sometimes dramatically. In some cases, bacteria, most often Propionibacterium acnes, have been cultured from bone biopsy specimens and occasionally other sites. IBD was coexistent in 8% of patients in one large series. B27 is not associated. Either bone scan or computed tomography scan is helpful diagnostically. An MRI report described characteristic vertebral body corner cortical erosions in 12 of 12 patients. High-dose NSAIDs may provide relief from bone pain. A number of uncontrolled series and case reports describe successful therapy with pamidronate or other bisphosphonates. Response to anti-TNF-α therapy has also been observed, although in a few cases this has been associated with a flare of skin manifestations. Successful prolonged antibiotic therapy has also been reported. Recent reports suggest a possible autoinflammatory pathogenesis and successful treatment with the IL-1 receptor antagonist anakinra.

CHAPTER 11

THE VASCULITIS SYNDROMES

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DEFINITION

Vasculitis is a clinicopathologic process characterized by inflammation of and damage to blood vessels. T e vessel lumen is usually compromised, and this is associated with ischemia of the tissues supplied by the involved vessel. A broad and heterogeneous group of syndromes may result from this process, since any type, size, and location of blood vessel may be involved. Vasculitis and its consequences may be the primary or sole manifestation of a disease; alternatively, vasculitis may be a secondary component of another disease. Vasculitis may be confined to a single organ, such as the skin, or it may simultaneously involve several organ systems.

CLASSIFICATION

A major feature of the vasculitic syndromes as a group is the fact that there is a great deal of heterogeneity at the same time as there is considerable overlap among them. T is heterogeneity and overlap in addition to a lack of understanding of the pathogenesis of these syndromes have been major impediments to the development of a coherent classification system for these diseases. **Table 11-1** lists the major vasculitis syndromes. T e distinguishing and overlapping features of these syndromes are discussed below.

PATHOPHYSIOLOGY AND PATHOGENESIS

Generally, most of the vasculitic syndromes are assumed to be mediated at least in part by immunopathogenic mechanisms that occur in response to certain antigenic stimuli. However, evidence supporting this hypothesis is for the most part indirect and may reflect epiphenomena as opposed to true causality. Furthermore, it is unknown why some individuals might develop vasculitis in response to certain antigenic stimuli, whereas others do not. It is likely that a number of factors are involved in the ultimate expression of a vasculitic syndrome. T ese include the genetic predisposition, environmental exposures, and the regulatory mechanisms associated with immune response to certain antigens. Although immune complex formation, antineutrophil cytoplasmic antibodies (ANCA), and pathogenic T lymphocyte responses **(Table 11-2)** have been among the prominent hypothesized mechanisms, it is likely that the pathogenesis of individual forms of vasculitis is complex and varied.

PATHOGENIC IMMUNE-COMPLEX FORMATION

Deposition of immune complexes was the first and most widely accepted pathogenic mechanism of vasculitis. However, the causal role of immune complexes has not been clearly established in most of the vasculitic syndromes. Circulating immune complexes need not result in deposition of the complexes in blood vessels with ensuing vasculitis, and many patients with active vasculitis do not have demonstrable circulating or deposited immune complexes. T e actual antigen contained in the immune complex has only rarely been identified in vasculitic syndromes. In this regard, hepatitis B antigen has been identified in both the circulating and deposited immune complexes in a subset of patients who have features of a systemic vasculitis, most notably in polyarteritis nodosa (see "Polyarteritis Nodosa," p. 167). Cryoglobulinemic vasculitis is strongly associated with hepatitis C virus infection; hepatitis C virions and hepatitis C virus antigen-antibody complexes have been identified in the cryoprecipitates of these patients (see "Cryoglobulinemic Vasculitis," p. 173).

T e mechanisms of tissue damage in immune complex–mediated vasculitis resemble those described

TABLE 11-1

VASCULITIS SYNDROMES

PRIMARY VASCULITIS SYNDROMES	SECONDARY VASCULITIS SYNDROMES
Granulomatosis with polyangiitis (Wegener's)	Vasculitis associated with probable etiology
Microscopic polyangiitis	Drug-induced vasculitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Hepatitis C virus–associated cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)	Hepatitis B virus–associated vasculitis
Cryoglobulinemic vasculitis	Cancer-associated vasculitis
Polyarteritis nodosa	Vasculitis associated with systemic disease
Kawasaki disease	Lupus vasculitis
Giant cell arteritis	Rheumatoid vasculitis
Takayasu arteritis	Sarcoid vasculitis
Behçet's disease	
Cogan's syndrome	
Single-organ vasculitis	
Cutaneous leukocytoclastic angiitis	
Cutaneous arteritis	
Primary central nervous system vasculitis	
Isolated aortitis	

Source: Adapted from JC Jennette et al: Arthritis Rheum 65:1, 2013.

for serum sickness. In this model, antigen-antibody complexes are formed in antigen excess and are deposited in vessel walls whose permeability has been increased by vasoactive amines such as histamine, bradykinin, and leukotrienes released from platelets or from mast cells as a result of IgE-triggered mechanisms.

TABLE 11-2

POTENTIAL MECHANISMS OF VESSEL DAMAGE IN VASCULITIS SYNDROMES

Pathogenic immune-complex formation and/or deposition
IgA vasculitis (Henoch-Schönlein)
Lupus vasculitis
Serum sickness and cutaneous vasculitis syndromes
Hepatitis C virus–associated cryoglobulinemic vasculitis
Hepatitis B virus–associated vasculitis
Production of antineutrophilic cytoplasmic antibodies
Granulomatosis with polyangiitis (Wegener's)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Pathogenic T lymphocyte responses and granuloma formation
Giant cell arteritis
Takayasu arteritis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Source: Adapted from MC Sneller, AS Fauci: Med Clin North Am 81:221, 1997.

The deposition of complexes results in activation of complement components, particularly C5a, which is strongly chemotactic for neutrophils. These cells then infiltrate the vessel wall, phagocytose the immune complexes, and release their intracytoplasmic enzymes, which damage the vessel wall. As the process becomes subacute or chronic, mononuclear cells infiltrate the vessel wall. The common denominator of the resulting syndrome is compromise of the vessel lumen with ischemic changes in the tissues supplied by the involved vessel. Several variables may explain why only certain types of immune complexes cause vasculitis and why only certain vessels are affected in individual patients. These include the ability of the reticuloendothelial system to clear circulating complexes from the blood, the size and physicochemical properties of immune complexes, the relative degree of turbulence of blood flow, the intravascular hydrostatic pressure in different vessels, and the preexisting integrity of the vessel endothelium.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCA)

ANCA are antibodies directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes. These autoantibodies are present in a high percentage of patients with active granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis, and in a lower percentage of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Because these diseases share the presence of ANCA and small-vessel vasculitis, some investigators have come to refer to them collectively as "ANCA-associated vasculitis." However, as these diseases possess unique clinical phenotypes in which ANCA may be absent, it remains our opinion that granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) should continue to be viewed as separate entities.

There are two major categories of ANCA based on different targets for the antibodies. The terminology of cytoplasmic ANCA (cANCA) refers to the diffuse, granular cytoplasmic staining pattern observed by immunofluorescence microscopy when serum antibodies bind to indicator neutrophils. Proteinase-3, a 29-kDa neutral serine proteinase present in neutrophil azurophilic granules, is the major cANCA antigen. More than 90% of patients with typical active granulomatosis with polyangiitis (Wegener's) have detectable antibodies to proteinase-3 (see below). The terminology of perinuclear ANCA (pANCA) refers to the more localized perinuclear or nuclear staining pattern of the indicator neutrophils. The major target for pANCA is the enzyme myeloperoxidase; other targets that can produce a pANCA pattern of staining include elastase, cathepsin G, lactoferrin,

lysozyme, and bactericidal/permeability-increasing protein. However, only antibodies to myeloperoxidase have been convincingly associated with vasculitis. Antimyeloperoxidase antibodies have been reported to occur in variable percentages of patients with microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), isolated necrotizing crescentic glomerulonephritis, and granulomatosis with polyangiitis (Wegener's) (see below). A pANCA pattern of staining that is not due to antimyeloperoxidase antibodies has been associated with nonvasculitic entities such as rheumatic and nonrheumatic autoimmune diseases, inflammatory bowel disease, certain drugs, and infections such as endocarditis and bacterial airway infections in patients with cystic fibrosis.

It is unclear why patients with these vasculitis syndromes develop antibodies to myeloperoxidase or proteinase-3 or what role these antibodies play in disease pathogenesis. T ere are a number of in vitro observations that suggest possible mechanisms whereby these antibodies can contribute to the pathogenesis of the vasculitis syndromes. Proteinase-3 and myeloperoxidase reside in the azurophilic granules and lysosomes of resting neutrophils and monocytes, where they are apparently inaccessible to serum antibodies. However, when neutrophils or monocytes are primed by tumor necrosis factor α (TNF-α) or interleukin 1 (IL-1), proteinase-3 and myeloperoxidase translocate to the cell membrane, where they can interact with extracellular ANCA. T e neutrophils then degranulate and produce reactive oxygen species that can cause tissue damage. Furthermore, ANCA-activated neutrophils can adhere to and kill endothelial cells in vitro. Activation of neutrophils and monocytes by ANCA also induces the release of proinflammatory cytokines such as IL-1 and IL-8. Adoptive transfer experiments in genetically engineered mice provide further evidence for a direct pathogenic role of ANCA in vivo. In contradiction, however, a number of clinical and laboratory observations argue against a primary pathogenic role for ANCA. Patients may have active granulomatosis with polyangiitis (Wegener's) in the absence of ANCA; the absolute height of the antibody titers does not correlate well with disease activity; and patients with granulomatosis with polyangiitis (Wegener's) in remission may continue to have high antiproteinase-3 (cANCA) titers for years (see below).

PATHOGENIC T LYMPHOCYTE RESPONSES AND GRANULOMA FORMATION

T e histopathologic feature of granulomatous vasculitis has provided evidence to support a role of pathogenic T lymphocyte responses and cell-mediated immune injury. Vascular endothelial cells can express HLA class II molecules following activation by cytokines such as interferon (IFN) γ. T is allows these cells to participate in immunologic reactions such as interaction with CD4+ T lymphocytes in a manner similar to antigen-presenting macrophages. Endothelial cells can secrete IL-1, which may activate T lymphocytes and initiate or propagate in situ immunologic processes within the blood vessel. In addition, IL-1 and TNF-α are potent inducers of endothelial-leukocyte adhesion molecule 1 (ELAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which may enhance the adhesion of leukocytes to endothelial cells in the blood vessel wall.

APPROACH TO THE PATIENT: General Principles of Diagnosis

T e diagnosis of vasculitis is often considered in any patient with an unexplained systemic illness. However, there are certain clinical abnormalities that when present alone or in combination should suggest a diagnosis of vasculitis. T ese include palpable purpura, pulmonary infiltrates and microscopic hematuria, chronic inflammatory sinusitis, mononeuritis multiplex, unexplained ischemic events, and glomerulonephritis with evidence of multisystem disease. A number of nonvasculitic diseases may also produce some or all of these abnormalities. T us, the first step in the workup of a patient with suspected vasculitis is to exclude other diseases that produce clinical manifestations that can mimic vasculitis **(Table 11-3)**. It is particularly important to exclude infectious diseases with features that overlap those of vasculitis, especially if the patient's clinical condition is deteriorating rapidly and empirical immunosuppressive treatment is being contemplated.

Once diseases that mimic vasculitis have been excluded, the workup should follow a series of progressive steps that establish the diagnosis of vasculitis and determine, where possible, the category of the vasculitis syndrome **(Fig. 11-1)**. T is approach is of considerable importance since several of the vasculitis syndromes require aggressive therapy with glucocorticoids and other immunosuppressive agents, whereas other syndromes usually resolve spontaneously and require symptomatic treatment only. T e definitive diagnosis of vasculitis is usually made based on biopsy of involved tissue. T e yield of "blind" biopsies of organs with no subjective or objective evidence of involvement is very low and should be avoided. When syndromes such as polyarteritis nodosa, Takayasu arteritis, or primary central nervous system (CNS) vasculitis are suspected, arteriogram of organs with suspected involvement should be performed.

GENERAL PRINCIPLES OF TREATMENT Once a diagnosis of vasculitis has been established, a decision regarding therapeutic strategy must be made (Fig. 11-1). If an offending

TABLE 11-3

CONDITIONS THAT CAN MIMIC VASCULITIS

- Infectious diseases
  - Bacterial endocarditis
  - Disseminated gonococcal infection
  - Pulmonary histoplasmosis
  - Coccidioidomycosis
  - Syphilis
  - Lyme disease
  - Rocky Mountain spotted fever
  - Whipple's disease
- Coagulopathies/thrombotic microangiopathies
  - Antiphospholipid syndrome
  - Thrombotic thrombocytopenic purpura
- Neoplasms
  - Atrial myxoma
  - Lymphoma
  - Carcinomatosis
- Drug toxicity
  - Cocaine
  - Levamisole
  - Amphetamines
  - Ergot alkaloids
  - Methysergide
  - Arsenic
- Sarcoidosis
- Atheroembolic disease
- Antiglomerular basement membrane disease (Goodpasture's syndrome)
- Amyloidosis
- Migraine
- Reversible cerebral vasoconstrictive syndrome
- Segmental arterial mediolysis (SAM) Collagen vascular disorders

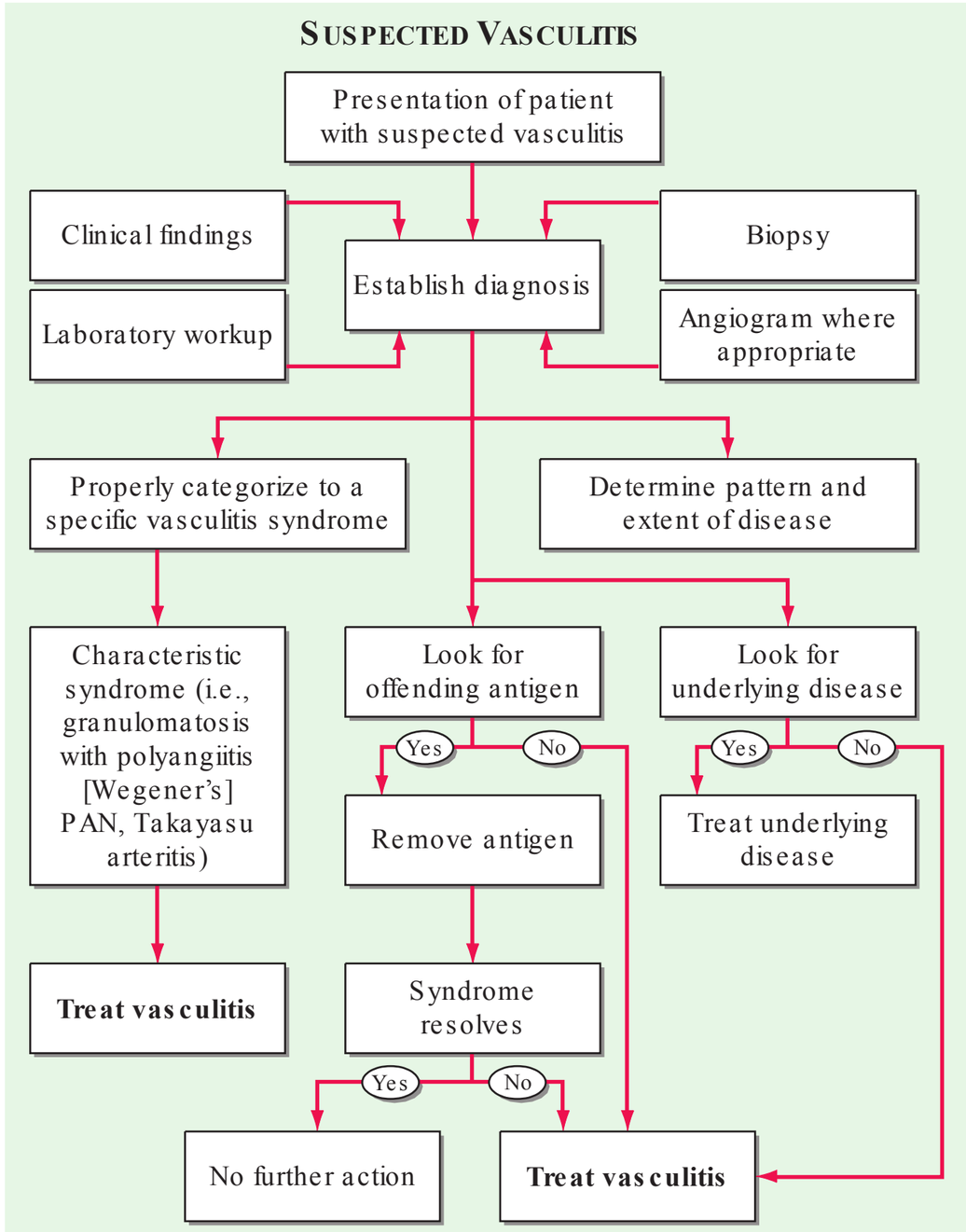


FIGURE 11-1
Algorithm for the approach to a patient with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

antigen that precipitates the vasculitis is recognized, the antigen should be removed where possible. If the vasculitis is associated with an underlying disease such as an infection, neoplasm, or connective tissue disease, the underlying disease should be treated. If the syndrome represents a primary vasculitic disease, treatment should be initiated according to the category of the vasculitis syndrome. Specific therapeutic regimens are discussed below for the individual vasculitis syndromes; however, certain general principles regarding therapy should be considered. Decisions regarding treatment should be based on the use of regimens for which there has been published literature supporting efficacy for that particular vasculitic disease. Since the potential toxic side effects of certain therapeutic regimens may be substantial, the risk-versus-benefit ratio of any therapeutic approach should be weighed carefully. On the one hand, glucocorticoids and/or other immunosuppressive agents should be instituted immediately in diseases where irreversible organ system dysfunction and high morbidity and mortality rates have been clearly established. Granulomatosis with polyangiitis (Wegener's) is the prototype of a severe systemic vasculitis requiring such a therapeutic approach (see below). On the other hand, when feasible, aggressive therapy should be avoided for vasculitic manifestations that rarely result in irreversible organ system dysfunction and that usually do not respond to such therapy. For example, isolated idiopathic cutaneous vasculitis usually resolves with symptomatic treatment, and prolonged courses of glucocorticoids uncommonly result in clinical benefit. Cytotoxic agents have not proved to be beneficial in idiopathic cutaneous vasculitis, and their toxic side effects generally outweigh any potential beneficial effects. Glucocorticoids should be initiated in those systemic vasculitides that cannot be specifically categorized or for which there is no established standard therapy; or other immunosuppressive therapy should be added in these diseases only if an adequate response does not result or if remission can only be achieved and maintained with an unacceptably toxic regimen of glucocorticoids. When remission is achieved, one should continually attempt to taper glucocorticoids and discontinue when possible. When using other immunosuppressive regimens, one should base the choice of agent upon the available therapeutic data supporting efficacy in that disease, the site and severity of organ involvement, and the toxicity profile of the drug.

TABLE 11-4

MAJOR TOXIC SIDE EFFECTS OF DRUGS USED IN THE TREATMENT OF SYSTEMIC VASCULITIS

Glucocorticoids	
Osteoporosis	Growth suppression in children
Cataracts	Hypertension
Glaucoma	Avascular necrosis of bone
Diabetes mellitus	Myopathy
Electrolyte abnormalities	Alterations in mood
Metabolic abnormalities	Psychosis
Suppression of inflammatory and immune responses leading to opportunistic infections	Pseudotumor cerebri
	Peptic ulcer diathesis
	Pancreatitis
Cushingoid features	
Cyclophosphamide	
Bone marrow suppression	Hypogammaglobulinemia
Cystitis	Pulmonary fibrosis
Bladder carcinoma	Myelodysplasia
Gonadal suppression	Oncogenesis
Gastrointestinal intolerance	Teratogenicity
	Opportunistic infections
Methotrexate	
Gastrointestinal intolerance	Pneumonitis
Stomatitis	Teratogenicity
Bone marrow suppression	Opportunistic infections
Hepatotoxicity (may lead to fibrosis or cirrhosis)	
Azathioprine	
Gastrointestinal intolerance	Opportunistic infections
Bone marrow suppression	Hypersensitivity
Hepatotoxicity	
Rituximab	
Infusion reactions	Opportunistic infections
Progressive multifocal leuko-encephalopathy	Hepatitis B reactivation
	Tumor lysis syndrome
Mucocutaneous reactions	

Physicians should be thoroughly aware of the toxic side effects of therapeutic agents employed that can include both acute and long-term complications **(Table 11-4)**. Morbidity and mortality can occur as a result of treatment, and strategies to monitor for and prevent toxicity represent an essential part of patient care. Glucocorticoids are an important part of treatment for most vasculitides but are associated with substantial toxicities. Monitoring and prevention of glucocorticoid-induced bone loss are important in all patients. With the use of daily cyclophosphamide, strategies are particularly important and are directed toward minimization of bladder toxicity and prevention of leukopenia. Instructing the patient to take cyclophosphamide all at once in the morning with a large amount of fluid throughout the day in order to maintain a dilute urine can reduce the risk of bladder injury. Bladder cancer can occur several years after discontinuation of cyclophosphamide therapy; therefore, monitoring for bladder cancer should continue indefinitely in patients who have received cyclophosphamide. Bone marrow suppression is an important toxicity of cyclophosphamide and can be observed during glucocorticoid tapering or over time, even after periods of stable measurements. Monitoring of the complete blood count every 1–2 weeks for as long as the patient receives cyclophosphamide can effectively prevent cytopenias. Maintaining the white blood cell (WBC) count at >3000/μL and the neutrophil count at >1500/μL is essential to reduce the risk of life-threatening infections.

Methotrexate and azathioprine are also associated with bone marrow suppression, and complete blood counts should be obtained every 1–2 weeks for the first 1–2 months after their initiation and once a month thereafter. To lessen toxicity, methotrexate is often given together with folic acid, 1 mg daily, or folinic acid, 5–10 mg once a week 24 h following methotrexate. Prior to initiation of azathioprine, thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of azathioprine, should be assayed because inadequate levels may result in severe cytopenia.

Infection represents a significant toxicity for all vasculitis patients treated with immunosuppressive therapy. Infections with Pneumocystis jiroveci and certain fungi can be seen even in the face of WBCs that are within normal limits, particularly in patients receiving glucocorticoids. All vasculitis patients who are receiving daily glucocorticoids in combination with another immunosuppressive agent should receive trimethoprim-sulfamethoxazole (TMP-SMX) or another prophylactic therapy to prevent P. jiroveci infection.

Finally, it should be emphasized that each patient is unique and requires individual decision-making. T e above outline should serve as a framework to guide therapeutic approaches; however, flexibility should be practiced in order to provide maximal therapeutic ef cacy with minimal toxic side effects in each patient.

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

DEFINITION

Granulomatosis with polyangiitis (Wegener's) is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur.

INCIDENCE AND PREVALENCE

Granulomatosis with polyangiitis (Wegener's) is an uncommon disease with an estimated prevalence of

3 per 100,000. It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1. T e disease can be seen at any age; □15% of patients are <19 years of age, but only rarely does the disease occur before adolescence; the mean age of onset is □40 years.

PATHOLOGY AND PATHOGENESIS

T e histopathologic hallmarks of granulomatosis with polyangiitis (Wegener's) are necrotizing vasculitis of small arteries and veins together with granuloma formation, which may be either intravascular or extravascular **(Fig. 11-2)**. Lung involvement typically appears as multiple, bilateral, nodular cavitary infiltrates **(Fig. 11-3)**, which on biopsy almost invariably reveal the typical necrotizing granulomatous vasculitis. Upper airway lesions, particularly those in the sinuses and nasopharynx, typically reveal inflammation, necrosis, and granuloma formation, with or without vasculitis.

In its earliest form, renal involvement is characterized by a focal and segmental glomerulitis that may evolve into a rapidly progressive crescentic glomerulonephritis. Granuloma formation is only rarely seen on renal biopsy. In contrast to other forms of glomerulonephritis, evidence of immune complex deposition is not found in the renal lesion of granulomatosis with polyangiitis (Wegener's). In addition to the classic triad of disease of the upper and lower respiratory tracts and kidney, virtually any organ can be involved with vasculitis, granuloma, or both.

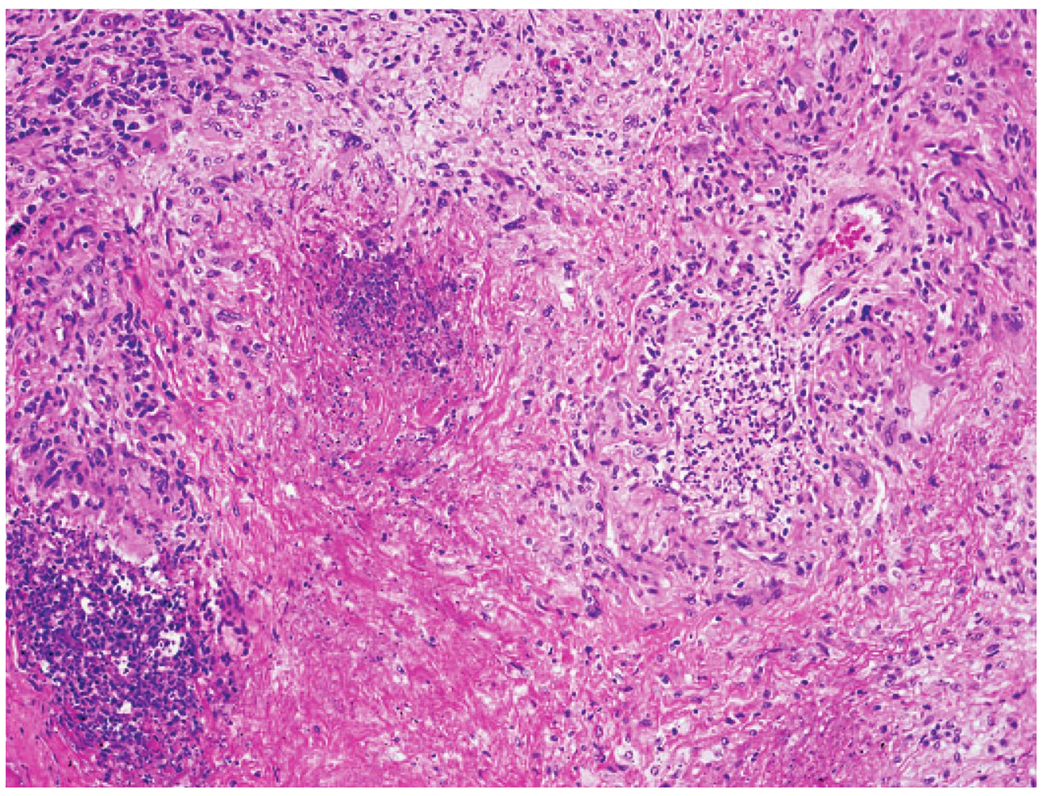


FIGURE 11-2
Lung histology in granulomatosis with polyangiitis (Wegener's). This area of geographic necrosis has a serpiginous border of histiocytes and giant cells surrounding a central necrotic zone. Vasculitis is also present with neutrophils and lymphocytes infiltrating the wall of a small arteriole (upper right). (Courtesy of William D. Travis, MD; with permission.)

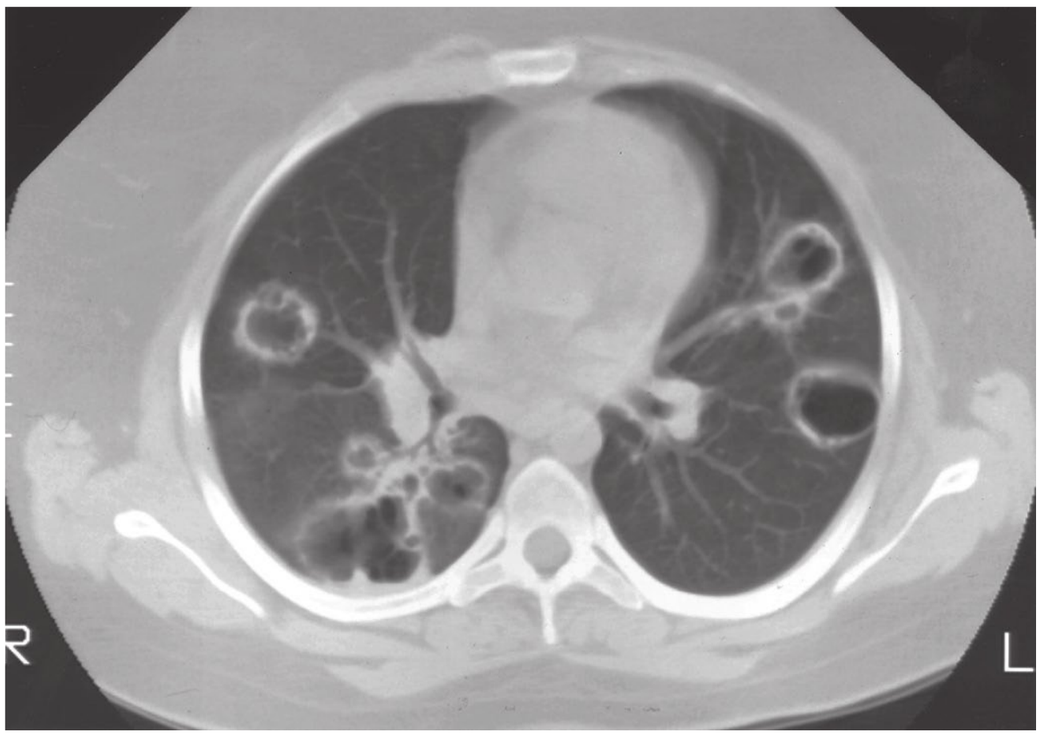


FIGURE 11-3
Computed tomography scan of a patient with granulomatosis with polyangiitis (Wegener's). The patient developed multiple, bilateral, and cavitary infiltrates.

T e immunopathogenesis of this disease is unclear, although the involvement of upper airways and lungs with granulomatous vasculitis suggests an aberrant cell-mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway. Chronic nasal carriage of Staphylococcus aureus has been reported to be associated with a higher relapse rate of granulomatosis with polyangiitis (Wegener's); however, there is no evidence for a role of this organism in the pathogenesis of the disease.

Peripheral blood mononuclear cells obtained from patients with granulomatosis with polyangiitis (Wegener's) manifest increased secretion of IFN-γ but not of IL-4, IL-5, or IL-10 compared to normal controls. In addition, TNF-α production from peripheral blood mononuclear cells and CD4+ T cells is elevated. Furthermore, monocytes from patients with granulomatosis with polyangiitis (Wegener's) produce increased amounts of IL-12. T ese findings indicate an unbalanced T_H1-type T cell cytokine pattern in this disease that may have pathogenic and perhaps ultimately therapeutic implications.

A high percentage of patients with granulomatosis with polyangiitis (Wegener's) develop ANCA, and these autoantibodies may play a role in the pathogenesis of this disease (see above).

CLINICAL AND LABORATORY MANIFESTATIONS

Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis (Wegener's). Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with or without nasal mucosal ulceration **(Table 11-5)**. Nasal septal perforation may follow, leading to saddle nose

TABLE 11-5

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S): FREQUENCY OF CLINICAL MANIFESTATIONS IN 158 PATIENTS STUDIED AT THE NATIONAL INSTITUTES OF HEALTH

MANIFESTATION	PERCENTAGE AT DISEASE ONSET	PERCENTAGE THROUGHOUT COURSE OF DISEASE
Kidney		
Glomerulonephritis	18	77
Ear/Nose/Throat	73	92
Sinusitis	51	85
Nasal disease	36	68
Otitis media	25	44
Hearing loss	14	42
Subglottic stenosis	1	16
Ear pain	9	14
Oral lesions	3	10
Lung	45	85
Pulmonary infiltrates	25	66
Pulmonary nodules	24	58
Hemoptysis	12	30
Pleuritis	10	28
Eyes		
Conjunctivitis	5	18
Dacryocystitis	1	18
Scleritis	6	16
Proptosis	2	15
Eye pain	3	11
Visual loss	0	8
Retinal lesions	0	4
Corneal lesions	0	1
Iritis	0	2
Other[a]		
Arthralgias/arthritis	32	67
Fever	23	50
Cough	19	46
Skin abnormalities	13	46
Weight loss (>10% body weight)	15	35
Peripheral neuropathy	1	15
Central nervous system disease	1	8
Pericarditis	2	6
Hyperthyroidism	1	3

[a]Fewer than 1% had parotid, pulmonary artery, breast, or lower genitourinary (urethra, cervix, vagina, testicular) involvement.
Source: GS Hoffman et al: Ann Intern Med 116:488, 1992.

deformity. Serous otitis media may occur as a result of eustachian tube blockage. Subglottic tracheal stenosis resulting from active disease or scarring occurs in □16% of patients and may result in severe airway obstruction.

Pulmonary involvement may be manifested as asymptomatic infiltrates or may be clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort. It is present in 85–90% of patients. Endobronchial disease, either in its active form or as a result of fibrous scarring, may lead to obstruction with atelectasis.

Eye involvement (52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions leading to proptosis.

Skin lesions (46% of patients) appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules; biopsy reveals vasculitis, granuloma, or both. Cardiac involvement (8% of patients) manifests as pericarditis, coronary vasculitis, or, rarely, cardiomyopathy. Nervous system manifestations (23% of patients) include cranial neuritis, mononeuritis multiplex, or, rarely, cerebral vasculitis and/or granuloma.

Renal disease (77% of patients) generally dominates the clinical picture and, if left untreated, accounts directly or indirectly for most of the mortality rate in this disease. Although it may smolder in some cases as a mild glomerulitis with proteinuria, hematuria, and red blood cell casts, it is clear that once clinically detectable renal functional impairment occurs, rapidly progressive renal failure usually ensues unless appropriate treatment is instituted.

While the disease is active, most patients have nonspecific symptoms and signs such as malaise, weakness, arthralgias, anorexia, and weight loss. Fever may indicate activity of the underlying disease but more often reflects secondary infection, usually of the upper airway.

Characteristic laboratory findings include a markedly elevated erythrocyte sedimentation rate (ESR), mild anemia and leukocytosis, mild hypergammaglobulinemia (particularly of the IgA class), and mildly elevated rheumatoid factor. T rombocytosis may be seen as an acute-phase reactant. Approximately 90% of patients with active granulomatosis with polyangiitis (Wegener's) have a positive antiproteinase-3 ANCA. However, in the absence of active disease, the sensitivity drops to □60–70%. A small percentage of patients with granulomatosis with polyangiitis (Wegener's) may have antimyeloperoxidase rather than antiproteinase-3 antibodies, and up to 20% may lack ANCA.

Patients with granulomatosis with polyangiitis (Wegener's) have been found to have an increased incidence of venous thrombotic events. Although routine anticoagulation for all patients is not recommended, a heightened awareness for any clinical features suggestive of deep venous thrombosis or pulmonary emboli is warranted.

DIAGNOSIS

T e diagnosis of granulomatosis with polyangiitis (Wegener's) is made by the demonstration of

necrotizing granulomatous vasculitis on tissue biopsy in a patient with compatible clinical features. Pulmonary tissue offers the highest diagnostic yield, almost invariably revealing granulomatous vasculitis. Biopsy of upper airway tissue usually reveals granulomatous inflammation with necrosis but may not show vasculitis. Renal biopsy can confirm the presence of pauci-immune glomerulonephritis.

T e specificity of a positive antiproteinase-3 ANCA for granulomatosis with polyangiitis (Wegener's) is very high, especially if active glomerulonephritis is present. However, the presence of ANCA should be adjunctive and, with rare exceptions, should not substitute for a tissue diagnosis. False-positive ANCA titers have been reported in certain infectious and neoplastic diseases.

In its typical presentation, the clinicopathologic complex of granulomatosis with polyangiitis (Wegener's) usually provides ready differentiation from other disorders. However, if all the typical features are not present at once, it needs to be differentiated from the other vasculitides, antiglomerular basement membrane disease (Goodpasture's syndrome), relapsing polychondritis **(Chap. 13)**, tumors of the upper airway or lung, and infectious diseases such as histoplasmosis, mucocutaneous leishmaniasis, and rhinoscleroma as well as noninfectious granulomatous diseases.

Of particular note is the differentiation from other midline destructive diseases. T ese diseases lead to extreme tissue destruction and mutilation localized to the midline upper airway structures including the sinuses; erosion through the skin of the face commonly occurs, a feature that is extremely rare in granulomatosis with polyangiitis (Wegener's). Although blood vessels may be involved in the intense inflammatory reaction and necrosis, primary vasculitis is not seen. Upper airway neoplasms and specifically extranodal natural killer (NK)/T cell lymphoma (nasal type) are important causes of midline destructive disease. T ese lesions are diagnosed based on histology, which reveals polymorphous atypical lymphoid cells with an NK cell immunophenotype, typically Epstein-Barr virus. Such cases are treated based on their degree of dissemination, and localized lesions have responded to irradiation. Upper airway lesions should never be irradiated in granulomatosis with polyangiitis (Wegener's). Cocaine-induced tissue injury can be another important mimic of granulomatosis with polyangiitis (Wegener's) in patients who present with isolated midline destructive disease. ANCA that target human neutrophil elastase can be found in patients with cocaine-induced midline destructive lesions and can complicate the differentiation from granulomatosis with polyangiitis (Wegener's). T is has been further confounded by the high frequency of levamisole adulteration of cocaine, which can result in cutaneous infarction and serologic changes that may mimic vasculitis. Granulocytopenia is a common finding in levamisole-induced disease that would not be associated with granulomatosis with polyangiitis (Wegener's).

Granulomatosis with polyangiitis (Wegener's) must also be differentiated from lymphomatoid granulomatosis, which is an Epstein-Barr virus–positive B cell proliferation that is associated with an exuberant T cell reaction. Lymphomatoid granulomatosis is characterized by lung, skin, CNS, and kidney involvement in which atypical lymphocytoid and plasmacytoid cells infiltrate nonlymphoid tissue in an angioinvasive manner. In this regard, it clearly differs from granulomatosis with polyangiitis (Wegener's) in that it is not an inflammatory vasculitis in the classic sense but an angiocentric perivascular infiltration of atypical mononuclear cells. Up to 50% of patients may develop a true malignant lymphoma.

TREATMENT Granulomatosis with Polyangiitis (Wegener's)

Prior to the introduction of effective therapy, granulomatosis with polyangiitis (Wegener's) was universally fatal within a few months of diagnosis. Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of the disease. T e development of treatment with cyclophosphamide dramatically changed patient outcome such that marked improvement was seen in >90% of patients, complete remission in 75% of patients, and 5-year patient survival was seen in over 80%.

Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. T e determination of relapse should be based on objective evidence of disease activity, taking care to rule out other features that may have a similar appearance such as infection, medication toxicity, or chronic disease sequelae. T e ANCA titer can be misleading and should not be used to assess disease activity. Many patients who achieve remission continue to have elevated titers for years. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% relapsed within 1 year of an increase in ANCA levels. T us, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy. Reinduction of remission after relapse is almost always achieved; however, a high percentage of patients ultimately have some degree of damage from irreversible features of their disease, such as varying degrees of renal insuf ciency, hearing loss, tracheal stenosis, saddle nose deformity, and chronically impaired sinus function. Patients who developed irreversible renal failure but who achieved subsequent remission have undergone successful renal transplantation.

Because long-term cyclophosphamide is associated with substantial toxicity, approaches have been developed that

seek to minimize the duration of exposure to cyclophosphamide while still taking advantage of its efficacy for severe disease. Treatment of granulomatosis with polyangiitis (Wegener's) is currently viewed as having two phases: induction, where active disease is put into remission, followed by maintenance. The decision regarding which agents to use for induction and maintenance is based on disease severity together with individual patient factors that include contraindication, relapse history, and comorbidities.

CYCLOPHOSPHAMIDE INDUCTION FOR SEVERE DISEASE For patients with severe disease, daily cyclophosphamide combined with glucocorticoids has been repeatedly proved to effectively induce remission and prolong survival. At the initiation of therapy, glucocorticoids are usually given as prednisone, 1 mg/kg per day for the first month, followed by gradual tapering on an alternate-day or daily schedule with discontinuation after 6–9 months.

Cyclophosphamide is given in doses of 2 mg/kg per day orally, but as it is renally eliminated, dosage reduction should be considered in patients with renal insufficiency. Some reports have indicated therapeutic success with less frequent and severe toxic side effects using IV cyclophosphamide. In a recent randomized trial, IV cyclophosphamide 15 mg/kg, three infusions given every 2 weeks, then every 3 weeks thereafter, was compared to cyclophosphamide 2 mg/kg daily given for 3 months followed by 1.5 mg/kg daily. Although IV cyclophosphamide was found to have a comparable rate of remission with a lower cumulative cyclophosphamide dose and occurrence of leukopenia, the use of a consolidation phase and an insufficient frequency of blood count monitoring may have negatively influenced the results in those who received daily cyclophosphamide. Of note in this study was that relapse occurred in 19% of those who received IV cyclophosphamide as compared to 9% who received daily oral administration. We continue to strongly favor daily cyclophosphamide with utilization of blood count monitoring every 1–2 weeks (as discussed above) and limiting the duration of induction exposure to 3–6 months.

In patients with imminently life-threatening disease, such as rapidly progressive glomerulonephritis with a creatinine greater than 4.0 mg/dL or pulmonary hemorrhage requiring mechanical ventilation, a regimen of daily cyclophosphamide and glucocorticoids is the treatment of choice to induce remission. Adjunctive plasmapheresis was found to further improve renal recovery in a study of patients with rapidly progressive glomerulonephritis who had a creatinine of greater than 5.8 mg/dL.

REMISSION MAINTENANCE AFTER CYCLOPHOSPHAMIDE After 3–6 months of induction treatment, cyclophosphamide should be stopped and switched to another agent for remission maintenance. The agents with which there has been the greatest published experience are methotrexate and azathioprine and more recently ritixumab (discussed later in this section). Methotrexate is administered orally or subcutaneously starting at a dosage of 0.3 mg/kg as a single weekly dose, not to exceed 15 mg/week. If the treatment is well tolerated after 1–2 weeks, the dosage should be increased by 2.5 mg weekly up to a dosage of 20–25 mg/week and maintained at that level. Azathioprine, 2 mg/kg per day, has also proved effective in maintaining remission following induction with daily cyclophosphamide. In a randomized trial comparing methotrexate to azathioprine for remission maintenance, comparable rates of toxicity and relapse were seen. Therefore, the choice of agent is often based on toxicity profile, because methotrexate cannot be given to patients with renal insufficiency or chronic liver disease, as well as on other individual patient factors. In patients who are unable to receive methotrexate or azathioprine or who have relapsed through such treatment, mycophenolate mofetil, 1000 mg twice a day, may also sustain remission following cyclophosphamide induction. Rituximab was compared to azathioprine for maintenance after remission induction with intravenous cyclophosphamide. In this study, rituximab was found to be associated with a lower rate of relapse. However, the short duration of this trial continues to raise questions as to the optimal approach to longer-term remission maintenance.

The optimal duration of maintenance therapy is uncertain. In the absence of toxicity, maintenance therapy is usually given for a minimum of 2 years past remission, after which time consideration can be given for tapering over a 6–12 month period until discontinuation. Patients with significant organ damage or a history of relapse may benefit from longer-term continuation of a maintenance agent.

RITUXIMAB INDUCTION FOR SEVERE DISEASE Rituximab is a chimeric monoclonal antibody directed against CD20 present on normal and malignant B lymphocytes that is U.S. Food and Drug Administration (FDA) approved for the treatment of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. In two randomized trials that enrolled ANCA-positive patients with severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, rituximab 375 mg/m^2 once a week for 4 weeks in combination with glucocorticoids was found to be as effective as cyclophosphamide with glucocorticoids for inducing disease remission. In the trial, which also enrolled patients with relapsing disease, rituximab was found to be statistically superior to cyclophosphamide.

Although the data support that rituximab is effective for remission induction of severe active granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis, there remain a number of ongoing questions regarding rituximab that must be considered in weighing its use in the individual patient. The optimal approach to remission maintenance after treatment with rituximab remains unclear, as does whether this should include conventional maintenance agents such as methotrexate or azathioprine versus scheduled retreatment with rituximab. In addition, there are no long-term safety data with rituximab in granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis.

Although rituximab does not have the bladder toxicity or infertility concerns, as can occur with cyclophosphamide, in

both of the randomized trials, the rate of adverse events was similar in the rituximab and cyclophosphamide arms. Serious side effects of rituximab include infusion reactions, severe mucocutaneous reactions, and rare reports of progressive multifocal leukoencephalopathy. Because rituximab can bring about reactivation of hepatitis B, all patients should undergo hepatitis screening prior to treatment with rituximab.

OTHER BIOLOGIC THERAPIES Etanercept, a dimeric fusion protein containing the 75-kDa TNF receptor bound to human IgG1, was not found to sustain remission when used adjunctively to standard therapy and should not be used in the treatment of granulomatosis with polyangiitis (Wegener's).

METHOTREXATE INDUCTION FOR NONSEVERE DISEASE For selected patients whose disease is not immediately life threatening, methotrexate together with glucocorticoids given at the dosages described above may be considered as an alternative for induction therapy, which is then continued for maintenance.

TRIMETHOPRIM-SULFAMETHOXAZOLE Although certain reports have indicated that TMP-SMX may be of benefit in the treatment of granulomatosis with polyangiitis (Wegener's) isolated to the sinonasal tissues, it should never be used alone to treat active granulomatosis with polyangiitis (Wegener's) outside of the upper airway such as in patients with renal or pulmonary disease. In a study examining the effect of TMP-SMX on relapse, decreased relapses were shown only with regard to upper airway disease, and no differences in major organ relapses were observed.

ORGAN-SPECIFIC TREATMENT Not all manifestations of granulomatosis with polyangiitis (Wegener's) require or respond to immunosuppressive therapy. In managing non–major organ disease, such as that isolated to the sinus, joints, or skin, the risks of treatment should be carefully weighed against the benefits. Treatment with cyclophosphamide is rarely if ever justified for the treatment of isolated sinus disease in granulomatosis with polyangiitis (Wegener's). Although patients with non–major organ disease may be effectively treated without immunosuppressive therapy, these individuals must be monitored closely for the development of disease activity affecting the lungs, kidneys, or other major organs. Subglottic stenosis and endobronchial stenosis are examples of disease manifestations that do not typically respond to systemic immunosuppressive treatment.

MICROSCOPIC POLYANGIITIS

DEFINITION

The term microscopic polyarteritis was introduced into the literature by Davson in 1948 in recognition of the presence of glomerulonephritis in patients with polyarteritis nodosa. In 1992, the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis adopted the term microscopic polyangiitis to connote a necrotizing vasculitis with few or no immune complexes affecting small vessels (capillaries, venules, or arterioles). Glomerulonephritis is very common in microscopic polyangiitis, and pulmonary capillaritis often occurs. The absence of granulomatous inflammation in microscopic polyangiitis is said to differentiate it from granulomatosis with polyangiitis (Wegener's).

INCIDENCE AND PREVALENCE

The incidence of microscopic polyangiitis has not yet been reliably established due to its previous inclusion as part of polyarteritis nodosa. The mean age of onset is 57 years of age, and males are slightly more frequently affected than females.

PATHOLOGY AND PATHOGENESIS

The vasculitis seen in microscopic polyangiitis has a predilection to involve capillaries and venules in addition to small and medium-sized arteries. Immunohistochemical staining reveals a paucity of immunoglobulin deposition in the vascular lesion of microscopic polyangiitis, suggesting that immune-complex formation does not play a role in the pathogenesis of this syndrome. The renal lesion seen in microscopic polyangiitis is identical to that of granulomatosis with polyangiitis (Wegener's). Like granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis is highly associated with the presence of ANCA, which may play a role in pathogenesis of this syndrome (see above).

CLINICAL AND LABORATORY MANIFESTATIONS

Because of its predilection to involve the small vessels, microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's) share similar clinical features. Disease onset may be gradual, with initial symptoms of fever, weight loss, and musculoskeletal pain; however, it is often acute. Glomerulonephritis occurs in at least 79% of patients and can be rapidly progressive, leading to renal failure. Hemoptysis may be the first symptom of alveolar hemorrhage, which occurs in 12% of patients. Other manifestations include mononeuritis multiplex and gastrointestinal tract and cutaneous vasculitis. Upper airway disease and pulmonary nodules are not typically found in microscopic polyangiitis and, if present, suggest granulomatosis with polyangiitis (Wegener's).

Features of inflammation may be seen, including an elevated ESR, anemia, leukocytosis, and thrombocytosis. ANCA are present in 75% of patients with microscopic polyangiitis, with antimyeloperoxidase antibodies being the predominant ANCA associated with this disease.

DIAGNOSIS

T e diagnosis is based on histologic evidence of vasculitis or pauci-immune glomerulonephritis in a patient with compatible clinical features of multisystem disease. Although microscopic polyangiitis is strongly ANCA-associated, no studies have as yet established the sensitivity and specificity of ANCA in this disease.

TREATMENT Microscopic Polyangiitis

T e 5-year survival rate for patients with treated microscopic polyangiitis is 74%, with disease-related mortality occurring from alveolar hemorrhage or gastrointestinal, cardiac, or renal disease. Studies on treatment have come from trials that have included patients with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis. Currently, the treatment approach for microscopic polyangiitis is the same as is used for granulomatosis with polyangiitis (Wegener's) (see "Granulomatosis with Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen), and patients with immediately life-threatening disease should be treated with the combination of prednisone and daily cyclophosphamide or rituximab. Disease relapse has been observed in at least 34% of patients. Treatment for such relapses would be similar to that used at the time of initial presentation and based on site and severity of disease.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS)

DEFINITION

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) was described in 1951 by Churg and Strauss and is characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and vasculitis of multiple organ systems.

INCIDENCE AND PREVALENCE

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is an uncommon disease with an estimated annual incidence of 1–3 per million. T e disease can occur at any age with the possible exception of infants. T e mean age of onset is 48 years, with a female-to-male ratio of 1.2:1.

PATHOLOGY AND PATHOGENESIS

T e necrotizing vasculitis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) involves small and medium-sized muscular arteries, capillaries, veins, and venules. A characteristic histopathologic feature of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is granulomatous reactions that may be present in the tissues or even within the walls of the vessels themselves. T ese are usually associated with infiltration of the tissues with eosinophils. T is process can occur in any organ in the body; lung involvement is predominant, with skin, cardiovascular system, kidney, peripheral nervous system, and gastrointestinal tract also commonly involved. Although the precise pathogenesis of this disease is uncertain, its strong association with asthma and its clinicopathologic manifestations, including eosinophilia, granuloma, and vasculitis, point to aberrant immunologic phenomena.

CLINICAL AND LABORATORY MANIFESTATIONS

Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) often exhibit nonspecific manifestations such as fever, malaise, anorexia, and weight loss, which are characteristic of a multisystem disease. T e pulmonary findings in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) clearly dominate the clinical picture with severe asthmatic attacks and the presence of pulmonary infiltrates. Mononeuritis multiplex is the second most common manifestation and occurs in up to 72% of patients. Allergic rhinitis and sinusitis develop in up to 61% of patients and are often observed early in the course of disease. Clinically recognizable heart disease occurs in □14% of patients and is an important cause of mortality. Skin lesions occur in □51% of patients and include purpura in addition to cutaneous and subcutaneous nodules. T e renal disease in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is less common and generally less severe than that of granulomatosis with polyangiitis and microscopic polyangiitis.

T e characteristic laboratory finding in virtually all patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is a striking eosinophilia, which reaches levels >1000 cells/μL in >80% of patients. Evidence of inflammation as evidenced by elevated ESR, fibrinogen, or α_2-globulins can be found in 81% of patients. T e other laboratory findings reflect the organ systems involved. Approximately 48% of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) have circulating ANCA that is usually antimyeloperoxidase.

DIAGNOSIS

Although the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is optimally made by biopsy in a patient with the characteristic clinical manifestations (see above), histologic confirmation can

be challenging because the pathognomonic features often do not occur simultaneously. In order to be diagnosed with eosinophilic granulomatosis with polyangiitis (Churg-Strauss), a patient should have evidence of asthma, peripheral blood eosinophilia, and clinical features consistent with vasculitis.

TREATMENT Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

The prognosis of untreated eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is poor, with a reported 5-year survival of 25%. With treatment, prognosis is favorable, with one study finding a 78-month actuarial survival rate of 72%. Myocardial involvement is the most frequent cause of death and is responsible for 39% of patient mortality. Echocardiography should be performed in all newly diagnosed patients because this may influence therapeutic decisions.

Glucocorticoids alone appear to be effective in many patients. Dosage tapering is often limited by asthma, and many patients require low-dose prednisone for persistent asthma many years after clinical recovery from vasculitis. In glucocorticoid failure or in patients who present with fulminant multisystem disease, particularly cardiac involvement, the treatment of choice is a combined regimen of daily cyclophosphamide and prednisone (see "Granulomatosis with Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen). Recent studies of mepolizumab (anti-IL-5 antibody) in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) have been encouraging, and this therapy is currently undergoing further investigation.

POLYARTERITIS NODOSA

DEFINITION

Polyarteritis nodosa was described in 1866 by Kussmaul and Maier. It is a multisystem, necrotizing vasculitis of small and medium-sized muscular arteries in which involvement of the renal and visceral arteries is characteristic. Polyarteritis nodosa does not involve pulmonary arteries, although bronchial vessels may be involved; granulomas, significant eosinophilia, and an allergic diathesis are not observed.

INCIDENCE AND PREVALENCE

It is difficult to establish an accurate incidence of polyarteritis nodosa because previous reports have included polyarteritis nodosa and microscopic polyangiitis as well as other related vasculitides. Polyarteritis nodosa, as currently defined, is felt to be a very uncommon disease.

PATHOLOGY AND PATHOGENESIS

The vascular lesion in polyarteritis nodosa is a necrotizing inflammation of small and medium-sized muscular arteries. The lesions are segmental and tend to involve bifurcations and branchings of arteries. They may spread circumferentially to involve adjacent veins. However, involvement of venules is not seen in polyarteritis nodosa and, if present, suggests microscopic polyangiitis (see below). In the acute stages of disease, polymorphonuclear neutrophils infiltrate all layers of the vessel wall and perivascular areas, which results in intimal proliferation and degeneration of the vessel wall. Mononuclear cells infiltrate the area as the lesions progress to the subacute and chronic stages. Fibrinoid necrosis of the vessels ensues with compromise of the lumen, thrombosis, infarction of the tissues supplied by the involved vessel, and, in some cases, hemorrhage. As the lesions heal, there is collagen deposition, which may lead to further occlusion of the vessel lumen. Aneurysmal dilations up to 1 cm in size along the involved arteries are characteristic of polyarteritis nodosa. Granulomas and substantial eosinophilia with eosinophilic tissue infiltrations are not characteristically found and suggest eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (see above).

Multiple organ systems are involved, and the clinicopathologic findings reflect the degree and location of vessel involvement and the resulting ischemic changes. As mentioned above, pulmonary arteries are not involved in polyarteritis nodosa, and bronchial artery involvement is uncommon. The pathology in the kidney in classic polyarteritis nodosa is that of arteritis without glomerulonephritis. In patients with significant hypertension, typical pathologic features of glomerulosclerosis may be seen. In addition, pathologic sequelae of hypertension may be found elsewhere in the body.

The presence of a polyarteritis nodosa–like vasculitis in patients with hepatitis B together with the isolation of circulating immune complexes composed of hepatitis B antigen and immunoglobulin, and the demonstration by immunofluorescence of hepatitis B antigen, IgM, and complement in the blood vessel walls, strongly suggest the role of immunologic phenomena in the pathogenesis of this disease. A polyarteritis nodosa–like vasculitis has also been reported in patients with hepatitis C. Hairy cell leukemia can be associated with polyarteritis nodosa; the pathogenic mechanisms of this association are unclear.

CLINICAL AND LABORATORY MANIFESTATIONS

Nonspecific signs and symptoms are the hallmarks of polyarteritis nodosa. Fever, weight loss, and malaise are present in over one-half of cases. Patients usually

TABLE 11-6

CLINICAL MANIFESTATIONS RELATED TO ORGAN SYSTEM INVOLVEMENT IN POLYARTERITIS NODOSA

ORGAN SYSTEM	PERCENT INCIDENCE	CLINICAL MANIFESTATIONS
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud's phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Source: From TR Cupps, AS Fauci: The Vasculitides. Philadelphia, Saunders, 1981.

present with vague symptoms such as weakness, malaise, headache, abdominal pain, and myalgias that can rapidly progress to a fulminant illness. Specific complaints related to the vascular involvement within a particular organ system may also dominate the presenting clinical picture as well as the entire course of the illness **(Table 11-6)**. In polyarteritis nodosa, renal involvement most commonly manifests as hypertension, renal insufficiency, or hemorrhage due to microaneurysms.

There are no diagnostic serologic tests for polyarteritis nodosa. In >75% of patients, the leukocyte count is elevated with a predominance of neutrophils. Eosinophilia is seen only rarely and, when present at high levels, suggests the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). The anemia of chronic disease may be seen, and an elevated ESR is almost always present. Other common laboratory findings reflect the particular organ involved. Hypergammaglobulinemia may be present, and all patients should be screened for hepatitis B and C. Antibodies against myeloperoxidase or proteinase-3 (ANCA) are rarely found in patients with polyarteritis nodosa.

DIAGNOSIS

The diagnosis of polyarteritis nodosa is based on the demonstration of characteristic findings of vasculitis on biopsy material of involved organs. In the absence of easily accessible tissue for biopsy, the arteriographic demonstration of involved vessels, particularly in the form of aneurysms of small and medium-sized arteries in the renal, hepatic, and visceral vasculature, is sufficient to make the diagnosis. This should consist of a catheter-directed dye arteriogram because magnetic resonance and computed tomography arteriograms do not have sufficient resolution at the current time to visualize the vessels affected in polyarteritis nodosa. Aneurysms of vessels are not pathognomonic of polyarteritis nodosa; furthermore, aneurysms need not always be present, and arteriographic findings may be limited to stenotic segments and obliteration of vessels. Biopsy of symptomatic organs such as nodular skin lesions, painful testes, and nerve/muscle provides the highest diagnostic yields.

TREATMENT Polyarteritis Nodosa

The prognosis of untreated polyarteritis nodosa is extremely poor, with a reported 5-year survival rate between 10 and 20%. Death usually results from gastrointestinal complications, particularly bowel infarcts and perforation, and cardiovascular causes. Intractable hypertension often compounds dysfunction in other organ systems, such as the kidneys, heart, and CNS, leading to additional late morbidity and mortality in polyarteritis nodosa. With the introduction of treatment, survival rate has increased substantially. Favorable therapeutic results have been reported in polyarteritis nodosa with the combination of prednisone and cyclophosphamide (see "Granulomatosis with Polyangiitis [Wegener's]" for a detailed description of this therapeutic regimen). In less severe cases of polyarteritis nodosa, glucocorticoids alone have resulted in disease remission. In patients with hepatitis B who have a polyarteritis nodosa–like vasculitis, antiviral therapy represents an important part of therapy and has been used in combination with glucocorticoids and plasma exchange. Careful attention to the treatment of hypertension can lessen the acute and late morbidity and mortality rates associated with renal, cardiac, and CNS complications of polyarteritis nodosa. Following successful treatment, relapse of polyarteritis nodosa has been estimated to occur in 10–20% of patients.

GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA

DEFINITION

Giant cell arteritis, historically referred to as temporal arteritis, is an inflammation of medium- and large-sized arteries. It characteristically involves one or more

branches of the carotid artery, particularly the temporal artery. However, it is a systemic disease that can involve arteries in multiple locations, particularly the aorta and its main branches.

Giant cell arteritis is closely associated with polymyalgia rheumatica, which is characterized by stiffness, aching, and pain in the muscles of the neck, shoulders, lower back, hips, and thighs. Most commonly, polymyalgia rheumatica occurs in isolation, but it may be seen in 40–50% of patients with giant cell arteritis. In addition, □10–20% of patients who initially present with features of isolated polymyalgia rheumatica later go on to develop giant cell arteritis. T is strong clinical association together with data from pathophysiologic studies has increasingly supported that giant cell arteritis and polymyalgia rheumatica represent differing clinical spectrums of a single disease process.

INCIDENCE AND PREVALENCE

Giant cell arteritis occurs almost exclusively in individuals >50 years. It is more common in women than in men and is rare in blacks. T e incidence of giant cell arteritis varies widely in different studies and in different geographic regions. A high incidence has been found in Scandinavia and in regions of the United States with large Scandinavian populations, compared to a lower incidence in southern Europe. T e annual incidence rates in individuals ≥50 years range from 6.9 to 32.8 per 100,000 population. Familial aggregation has been reported, as has an association with HLA-DR4. In addition, genetic linkage studies have demonstrated an association of giant cell arteritis with alleles at the HLA-DRB1 locus, particularly HLA-DRB1*04 variants. In Olmsted County, Minnesota, the annual incidence of polymyalgia rheumatica in individuals ≥50 years is 58.7 per 100,000 population.

PATHOLOGY AND PATHOGENESIS

Although the temporal artery is most frequently involved in giant cell arteritis, patients often have a systemic vasculitis of multiple medium- and large-sized arteries, which may go undetected. Histopathologically, the disease is a panarteritis with inflammatory mononuclear cell infiltrates within the vessel wall with frequent giant cell formation.T ere is proliferation of the intima and fragmentation of the internal elastic lamina. Pathophysiologic findings in organs result from the ischemia related to the involved vessels.

Experimental data support that giant cell arteritis is an antigen-driven disease in which activated T lymphocytes, macrophages, and dendritic cells play a critical role in the disease pathogenesis. Sequence analysis of the T cell receptor of tissue-infiltrating T cells in lesions of giant cell arteritis indicates restricted clonal expansion, suggesting the presence of an antigen residing in the arterial wall. Giant cell arteritis is believed to be initiated in the adventitia where CD4+ T cells enter through the vasa vasorum, become activated, and orchestrate macrophage differentiation. T cells recruited to vasculitic lesions in patients with giant cell arteritis produce predominantly IL-2 and IFN-γ, and the latter has been suggested to be involved in the progression to overt arteritis. Recent data demonstrate that at least two separate lineages of CD4 T cells—IFN-γ-producing T_H1 cells and IL-17-producing T_H17 cells—participate in vascular inflammation and may have differing levels of responsiveness to glucocorticoids.

CLINICAL AND LABORATORY MANIFESTATIONS

Giant cell arteritis is most commonly characterized clinically by the complex of fever, anemia, high ESR, and headaches in a patient over the age of 50 years. Other phenotypic manifestations include features of systemic inflammation including malaise, fatigue, anorexia, weight loss, sweats, arthralgias, polymyalgia rheumatica, or large-vessel disease.

In patients with involvement of the cranial arteries, headache is the predominant symptom and may be associated with a tender, thickened, or nodular artery, which may pulsate early in the disease but may become occluded later. Scalp pain and claudication of the jaw and tongue may occur. A well-recognized and dreaded complication of giant cell arteritis, particularly in untreated patients, is ischemic optic neuropathy, which may lead to serious visual symptoms, even sudden blindness in some patients. However, most patients have complaints relating to the head or eyes before visual loss. Attention to such symptoms with institution of appropriate therapy (see below) will usually avoid this complication. Other cranial ischemic complications include strokes and scalp or tongue infarction.

Up to one-third of patients can have large-vessel disease that can be the primary presentation of giant cell arteritis or can emerge at a later point in patients who have had previous cranial arteritis features or polymyalgia rheumatica. Manifestations of large-vessel disease can include subclavian artery stenosis that can present as arm claudication or aortic aneurysms involving the thoracic and to a lesser degree the abdominal aorta, which carry risks of rupture or dissection.

Characteristic laboratory findings in addition to the elevated ESR include a normochromic or slightly hypochromic anemia. Liver function abnormalities are common, particularly increased alkaline phosphatase levels. Increased levels of IgG and complement have

been reported. Levels of enzymes indicative of muscle damage such as serum creatine kinase are not elevated.

DIAGNOSIS

T e diagnosis of giant cell arteritis and its associated clinicopathologic syndrome can often be suggested clinically by the demonstration of the complex of fever, anemia, and high ESR with or without symptoms of polymyalgia rheumatica in a patient >50 years. T e diagnosis is confirmed by biopsy of the temporal artery. Since involvement of the vessel may be segmental, positive yield is increased by obtaining a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens. Ultrasonography of the temporal artery has been reported to be helpful in diagnosis. A temporal artery biopsy should be obtained as quickly as possible in the setting of ocular signs and symptoms, and under these circumstances, therapy should not be delayed pending a biopsy. In this regard, it has been reported that temporal artery biopsies may show vasculitis even after □14 days of glucocorticoid therapy. A dramatic clinical response to a trial of glucocorticoid therapy can further support the diagnosis.

Large-vessel disease may be suggested by symptoms and findings on physical examination such as diminished pulses or bruits. It is confirmed by vascular imaging, most commonly through magnetic resonance or computed tomography.

Isolated polymyalgia rheumatica is a clinical diagnosis made by the presence of typical symptoms of stiffness, aching, and pain in the muscles of the hip and shoulder girdle, an increased ESR, the absence of clinical features suggestive of giant cell arteritis, and a prompt therapeutic response to low-dose prednisone.

TREATMENT Giant Cell Arteritis and Polymyalgia Rheumatica

Acute disease-related mortality directly from giant cell arteritis is very uncommon, with fatalities occurring from cerebrovascular events or myocardial infarction. However, patients are at risk of late mortality from aortic aneurysm rupture or dissection as patients with giant cell arteritis are 18 times more likely to develop thoracic aortic aneurysms than the general population.

T e goals of treatment in giant cell arteritis are to reduce symptoms and, most importantly, to prevent visual loss. T e treatment approach for cranial and large-vessel disease in giant cell arteritis is currently the same. Giant cell arteritis and its associated symptoms are exquisitely sensitive to glucocorticoid therapy. Treatment should begin with prednisone, 40–60 mg/d for □1 month, followed by a gradual tapering. When ocular signs and symptoms occur, consideration should be given for the use of methylprednisolone 1000 mg daily for 3 days to protect remaining vision. Although the optimal duration of glucocorticoid therapy has not been established, most series have found that patients require treatment for ≥2 years. Symptom recurrence during prednisone tapering develops in 60–85% of patients with giant cell arteritis, requiring a dosage increase. T e ESR can serve as a useful indicator of inflammatory disease activity in monitoring and tapering therapy and can be used to judge the pace of the tapering schedule. However, minor increases in the ESR can occur as glucocorticoids are being tapered and do not necessarily reflect an exacerbation of arteritis, particularly if the patient remains symptom-free. Under these circumstances, the tapering should continue with caution. Glucocorticoid toxicity occurs in 35–65% of patients and represents an important cause of patient morbidity. Aspirin 81 mg daily has been found to reduce the occurrence of cranial ischemic complications in giant cell arteritis and should be given in addition to glucocorticoids in patients who do not have contraindications. T e use of weekly methotrexate as a glucocorticoid-sparing agent has been examined in two randomized placebo-controlled trials that reached conflicting conclusions. Infliximab, a monoclonal antibody to TNF, was studied in a randomized trial and was not found to provide benefit. Recent reports including a randomized trial have shown favorable response of giant cell arteritis to tocilizumab (anti-IL-6 receptor).

Patients with isolated polymyalgia rheumatica respond promptly to prednisone, which can be started at a lower dose of 10–20 mg/d. Similar to giant cell arteritis, the ESR can serve as a useful indicator in monitoring and prednisone reduction. Recurrent polymyalgia symptoms develop in the majority of patients during prednisone tapering. One study of weekly methotrexate found that the use of this drug reduced the prednisone dose on average by only 1 mg and did not decrease prednisone-related side effects. A randomized trial in polymyalgia rheumatica did not find infliximab to lessen relapse or glucocorticoid requirements.

TAKAYASU ARTERITIS

DEFINITION

Takayasu arteritis is an inflammatory and stenotic disease of medium- and large-sized arteries characterized by a strong predilection for the aortic arch and its branches.

INCIDENCE AND PREVALENCE

Takayasu arteritis is an uncommon disease with an estimated annual incidence rate of 1.2–2.6 cases per million. It is most prevalent in adolescent girls and young

women. Although it is more common in Asia, it is neither racially nor geographically restricted.

PATHOLOGY AND PATHOGENESIS

The disease involves medium- and large-sized arteries, with a strong predilection for the aortic arch and its branches; the pulmonary artery may also be involved. The most commonly affected arteries seen by arteriography are listed in **Table 11-7**. The involvement of the major branches of the aorta is much more marked at their origin than distally. The disease is a panarteritis with inflammatory mononuclear cell infiltrates and occasionally giant cells. There are marked intimal proliferation and fibrosis, scarring and vascularization of the media, and disruption and degeneration of the elastic lamina. Narrowing of the lumen occurs with or without thrombosis. The vasa vasorum are frequently involved. Pathologic changes in various organs reflect the compromise of blood flow through the involved vessels.

TABLE 11-7

FREQUENCY OF ARTERIOGRAPHIC ABNORMALITIES AND POTENTIAL CLINICAL MANIFESTATIONS OF ARTERIAL INVOLVEMENT IN TAKAYASU ARTERITIS

ARTERY	PERCENTAGE OF ARTERIOGRAPHIC ABNORMALITIES	POTENTIAL CLINICAL MANIFESTATIONS
Subclavian	93	Arm claudication, Raynaud's phenomenon
Common carotid	58	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta[a]	47	Abdominal pain, nausea, vomiting
Renal	38	Hypertension, renal failure
Aortic arch or root	35	Aortic insufficiency, congestive heart failure
Vertebral	35	Visual changes, dizziness
Coeliac axis[a]	18	Abdominal pain, nausea, vomiting
Superior mesenteric[a]	18	Abdominal pain, nausea, vomiting
Iliac	17	Leg claudication
Pulmonary	10–40	Atypical chest pain, dyspnea
Coronary	<10	Chest pain, myocardial infarction

[a]Arteriographic lesions at these locations are usually asymptomatic but may potentially cause these symptoms.
Source: G Kerr et al: Ann Intern Med 120:919, 1994.

Immunopathogenic mechanisms, the precise nature of which is uncertain, are suspected in this disease. As with several of the vasculitis syndromes, circulating immune complexes have been demonstrated, but their pathogenic significance is unclear.

CLINICAL AND LABORATORY MANIFESTATIONS

Takayasu arteritis is a systemic disease with generalized as well as vascular symptoms. The generalized symptoms include malaise, fever, night sweats, arthralgias, anorexia, and weight loss, which may occur months before vessel involvement is apparent. These symptoms may merge into those related to vascular compromise and organ ischemia. Pulses are commonly absent in the involved vessels, particularly the subclavian artery. The frequency of arteriographic abnormalities and the potentially associated clinical manifestations are listed in Table 11-7. Hypertension occurs in 32–93% of patients and contributes to renal, cardiac, and cerebral injury.

Characteristic laboratory findings include an elevated ESR, mild anemia, and elevated immunoglobulin levels.

DIAGNOSIS

The diagnosis of Takayasu arteritis should be suspected strongly in a young woman who develops a decrease or absence of peripheral pulses, discrepancies in blood pressure, and arterial bruits. The diagnosis is confirmed by the characteristic pattern on arteriography, which includes irregular vessel walls, stenosis, poststenotic dilation, aneurysm formation, occlusion, and evidence of increased collateral circulation. Complete aortic arteriography by catheter-directed dye arteriography or magnetic resonance arteriography should be obtained in order to fully delineate the distribution and degree of arterial disease. Histopathologic demonstration of vessel wall inflammation that is predominantly lymphocytic with granuloma formation and giant cells involving the media and adventitia adds confirmatory data; however, tissue is rarely readily available for examination. IgG4-related disease is a potential cause of aortitis and periaortitis that is histologically differentiated from Takayasu arteritis by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, a storiform pattern of fibrosis, and obliterative phlebitis **(Chap. 15)**.

TREATMENT Takayasu Arteritis

The long-term outcome of patients with Takayasu arteritis has varied widely between studies. Although two North American

reports found overall survival to be ≥94%, the 5-year mortality rate from other studies has ranged from 0 to 35%. Disease-related mortality most often occurs from congestive heart failure, cerebrovascular events, myocardial infarction, aneurysm rupture, or renal failure. Even in the absence of life-threatening disease, Takayasu arteritis can be associated with significant morbidity. T e course of the disease is variable, and although spontaneous remissions may occur, Takayasu arteritis is most often chronic and relapsing. Although glucocorticoid therapy in doses of 40–60 mg prednisone per day alleviates symptoms, there are no convincing studies that indicate that it increases survival. T e combination of glucocorticoid therapy for acute signs and symptoms and an aggressive surgical and/or arterioplastic approach to stenosed vessels has markedly improved outcome and decreased morbidity by lessening the risk of stroke, correcting hypertension due to renal artery stenosis, and improving blood flow to ischemic viscera and limbs. Unless it is urgently required, surgical correction of stenosed arteries should be undertaken only when the vascular inflammatory process is well controlled with medical therapy. In individuals who are refractory to or unable to taper glucocorticoids, methotrexate in doses up to 25 mg per week has yielded encouraging results. Preliminary results with anti-TNF therapies have been encouraging, but will require further study through randomized trials to determine ef cacy. T ere have been case-reports and retrospective cohorts reporting a favorable experience with tocilizumab (anti-IL6) but further experience is need before applying use in clinical practice.

IgA VASCULITIS (HENOCH-SCHÖNLEIN)

DEFINITION

IgA vasculitis (Henoch-Schönlein) is a small-vessel vasculitis characterized by palpable purpura (most commonly distributed over the buttocks and lower extremities), arthralgias, gastrointestinal signs and symptoms, and glomerulonephritis.

INCIDENCE AND PREVALENCE

IgA vasculitis (Henoch-Schönlein) is usually seen in children; most patients range in age from 4 to 7 years; however, the disease may also be seen in infants and adults. It is not a rare disease; in one series it accounted for between 5 and 24 admissions per year at a pediatric hospital. T e male-to-female ratio is 1.5:1. A seasonal variation with a peak incidence in spring has been noted.

PATHOLOGY AND PATHOGENESIS

The presumptive pathogenic mechanism for IgA (Henoch-Schönlein) vasculitis is immune-complex deposition. A number of inciting antigens have been suggested including upper respiratory tract infections, various drugs, foods, insect bites, and immunizations. IgA is the antibody class most often seen in the immune complexes and has been demonstrated in the renal biopsies of these patients.

CLINICAL AND LABORATORY MANIFESTATIONS

In pediatric patients, palpable purpura is seen in virtually all patients; most patients develop polyarthralgias in the absence of frank arthritis. Gastrointestinal involvement, which is seen in almost 70% of pediatric patients, is characterized by colicky abdominal pain usually associated with nausea, vomiting, diarrhea, or constipation and is frequently accompanied by the passage of blood and mucus per rectum; bowel intussusception may occur. Renal involvement occurs in 10–50% of patients and is usually characterized by mild glomerulonephritis leading to proteinuria and microscopic hematuria, with red blood cell casts in the majority of patients; it usually resolves spontaneously without therapy. Rarely, a progressive glomerulonephritis will develop. In adults, presenting symptoms are most frequently related to the skin and joints, while initial complaints related to the gut are less common. Although certain studies have found that renal disease is more frequent and more severe in adults, this has not been a consistent finding. However, the course of renal disease in adults may be more insidious and thus requires close follow-up. Myocardial involvement can occur in adults but is rare in children.

Laboratory studies generally show a mild leukocytosis, a normal platelet count, and occasionally eosinophilia. Serum complement components are normal, and IgA levels are elevated in about one-half of patients.

DIAGNOSIS

T e diagnosis of IgA vasculitis (Henoch-Schönlein) is based on clinical signs and symptoms. Skin biopsy specimen can be useful in confirming leukocytoclastic vasculitis with IgA and C3 deposition by immunofluorescence. Renal biopsy is rarely needed for diagnosis but may provide prognostic information in some patients.

TREATMENT IgA Vasculitis (Henoch-Schönlein)

T e prognosis of IgA vasculitis (Henoch-Schönlein) is excellent. Mortality is exceedingly rare, and 1–5% of children progress to end-stage renal disease. Most patients recover completely, and some do not require therapy. Treatment is similar for adults and children. When glucocorticoid therapy is required, prednisone, in doses of 1 mg/kg per day and tapered according to clinical response, has been shown to be useful in decreasing tissue edema, arthralgias, and abdominal

discomfort; however, it has not proved beneficial in the treatment of skin or renal disease and does not appear to shorten the duration of active disease or lessen the chance of recurrence. Patients with rapidly progressive glomerulonephritis have been anecdotally reported to benefit from intensive plasma exchange combined with cytotoxic drugs. Disease recurrences have been reported in 10–40% of patients.

CRYOGLOBULINEMIC VASCULITIS

DEFINITION

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins. Cryoglobulinemia may be associated with a systemic vasculitis characterized by palpable purpura, arthralgias, weakness, neuropathy, and glomerulonephritis. Although this can be observed in association with a variety of underlying disorders including multiple myeloma, lymphoproliferative disorders, connective tissue diseases, infection, and liver disease, in many instances it appears to be idiopathic. Because of the apparent absence of an underlying disease and the presence of cryoprecipitate containing oligoclonal/polyclonal immunoglobulins, this entity was referred to as essential mixed cryoglobulinemia. Since the discovery of hepatitis C, it has been established that the vast majority of patients who were considered to have essential mixed cryoglobulinemia have cryoglobulinemic vasculitis related to hepatitis C infection.

INCIDENCE AND PREVALENCE

T e incidence of cryoglobulinemic vasculitis has not been established. It has been estimated, however, that 5% of patients with chronic hepatitis C will develop cryoglobulinemic vasculitis.

PATHOLOGY AND PATHOGENESIS

Skin biopsies in cryoglobulinemic vasculitis reveal an inflammatory infiltrate surrounding and involving blood vessel walls, with fibrinoid necrosis, endothelial cell hyperplasia, and hemorrhage. Deposition of immunoglobulin and complement is common. Abnormalities of uninvolved skin including basement membrane alterations and deposits in vessel walls may be found. Membranoproliferative glomerulonephritis is responsible for 80% of all renal lesions in cryoglobulinemic vasculitis.

T e association between hepatitis C and cryoglobulinemic vasculitis has been supported by the high frequency of documented hepatitis C infection, the presence of hepatitis C RNA and anti–hepatitis C antibodies in serum cryoprecipitates, evidence of hepatitis C antigens in vasculitic skin lesions, and the effectiveness of antiviral therapy (see below). Current evidence suggests that in the majority of cases, cryoglobulinemic vasculitis occurs when an aberrant immune response to hepatitis C infection leads to the formation of immune complexes consisting of hepatitis C antigens, polyclonal hepatitis C–specific IgG, and monoclonal IgM rheumatoid factor. T e deposition of these immune complexes in blood vessel walls triggers an inflammatory cascade that results in cryoglobulinemic vasculitis.

CLINICAL AND LABORATORY MANIFESTATIONS

T e most common clinical manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. Renal disease develops in 10–30% of patients. Life-threatening rapidly progressive glomerulonephritis or vasculitis of the CNS, gastrointestinal tract, or heart occurs infrequently.

T e presence of circulating cryoprecipitates is the fundamental finding in cryoglobulinemic vasculitis. Rheumatoid factor is almost always found and may be a useful clue to the disease when cryoglobulins are not detected. Hypocomplementemia occurs in 90% of patients. An elevated ESR and anemia occur frequently. Evidence for hepatitis C infection must be sought in all patients by testing for hepatitis C antibodies and hepatitis C RNA.

TREATMENT Cryoglobulinemic Vasculitis

Acute mortality directly from cryoglobulinemic vasculitis is uncommon, but the presence of glomerulonephritis is a poor prognostic sign for overall outcome. In such patients, 15% progress to end-stage renal disease, with 40% later experiencing fatal cardiovascular disease, infection, or liver failure. As indicated above, the majority of cases are associated with hepatitis C infection. In such patients, treatment with antiviral therapy can prove beneficial and should be considered first-line therapy for hepatitis C–associated cryoglobulinemic vasculitis. Clinical improvement with antiviral therapy is dependent on the virologic response. Patients who clear hepatitis C from the blood have objective improvement in their vasculitis along with significant reductions in levels of circulating cryoglobulins, IgM, and rheumatoid factor. However, for those patients who do not have a sustained virologic response the vasculitis typically relapses with the return of viremia. While transient improvement can be observed with glucocorticoids, a complete response is seen in only 7% of patients. Plasmapheresis and cytotoxic agents have been used in anecdotal reports. T ese observations have not been confirmed, and such therapies carry significant risks. Randomized trials with rituximab (anti-CD20) in hepatitis C–associated cryoglobulinemic vasculitis have

provided evidence of benefit such that this agent should be considered in patients with active vasculitis either in combination with antiviral therapy or alone in patients who have relapsed through, are intolerant to, or have contraindications to antiviral agents.

SINGLE-ORGAN VASCULITIS

T e potential for vasculitis to affect single organs has become increasingly recognized. T is has been defined as vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis. Examples include isolated aortitis, testicular vasculitis, vasculitis of the breast, isolated cutaneous vasculitis, and primary CNS vasculitis. In some instances, this may be discovered at the time of surgery such as orchiectomy for a testicular mass where there is concern for neoplasm that is found instead to be vasculitis. Some patients originally diagnosed with single-organ vasculitis may later develop additional manifestations of a more systemic disease. In instances where there is no evidence of systemic vasculitis and the affected organ has been removed in its entirety, the patient may be followed closely without immunosuppressive therapy. In other instances, such as primary CNS vasculitis or some patients with isolated cutaneous vasculitis, medical intervention is warranted.

IDIOPATHIC CUTANEOUS VASCULITIS

DEFINITION

T e term cutaneous vasculitis is defined broadly as inflammation of the blood vessels of the dermis. Due to its heterogeneity, cutaneous vasculitis has been described by a variety of terms including hypersensitivity vasculitis and cutaneous leukocytoclastic angiitis. However, cutaneous vasculitis is not one specific disease but a manifestation that can be seen in a variety of settings. In >70% of cases, cutaneous vasculitis occurs either as part of a primary systemic vasculitis or as a secondary vasculitis related to an inciting agent or an underlying disease (see "Secondary Vasculitis," below). In the remaining 30% of cases, cutaneous vasculitis occurs idiopathically.

INCIDENCE AND PREVALENCE

Cutaneous vasculitis represents the most commonly encountered vasculitis in clinical practice. T e exact incidence of idiopathic cutaneous vasculitis has not been determined due to the predilection for cutaneous vasculitis to be associated with an underlying process and the variability of its clinical course.

PATHOLOGY AND PATHOGENESIS

T e typical histopathologic feature of cutaneous vasculitis is the presence of vasculitis of small vessels. Postcapillary venules are the most commonly involved vessels; capillaries and arterioles may be involved less frequently. T is vasculitis is characterized by a leukocytoclasis, a term that refers to the nuclear debris remaining from the neutrophils that have infiltrated in and around the vessels during the acute stages. In the subacute or chronic stages, mononuclear cells predominate; in certain subgroups, eosinophilic infiltration is seen. Erythrocytes often extravasate from the involved vessels, leading to palpable purpura. Cutaneous arteritis can also occur, which involves slightly larger-sized vessels within the dermis.

CLINICAL AND LABORATORY MANIFESTATIONS

T e hallmark of idiopathic cutaneous vasculitis is the predominance of skin involvement. Skin lesions may appear typically as palpable purpura; however, other cutaneous manifestations of the vasculitis may occur, including macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. T e skin lesions may be pruritic or even quite painful, with a burning or stinging sensation. Lesions most commonly occur in the lower extremities in ambulatory patients or in the sacral area in bedridden patients due to the effects of hydrostatic forces on the postcapillary venules. Edema may accompany certain lesions, and hyperpigmentation often occurs in areas of recurrent or chronic lesions.

T ere are no specific laboratory tests diagnostic of idiopathic cutaneous vasculitis. A mild leukocytosis with or without eosinophilia is characteristic, as is an elevated ESR. Laboratory studies should be aimed toward ruling out features to suggest an underlying disease or a systemic vasculitis.

DIAGNOSIS

T e diagnosis of cutaneous vasculitis is made by the demonstration of vasculitis on biopsy. An important diagnostic principle in patients with cutaneous vasculitis is to search for an etiology of the vasculitis—be it an exogenous agent, such as a drug or an infection, or an endogenous condition, such as an underlying disease (Fig. 11-1). In addition, a careful physical and laboratory examination should be performed to rule out the possibility of systemic vasculitis. T is should start with the least invasive diagnostic approach and proceed to the more invasive only if clinically indicated.

TREATMENT Idiopathic Cutaneous Vasculitis

When an antigenic stimulus is recognized as the precipitating factor in the cutaneous vasculitis, it should be removed; if this is a microbe, appropriate antimicrobial therapy should be instituted. If the vasculitis is associated with another underlying disease, treatment of the latter often results in resolution of the former. In situations where disease is apparently self-limited, no therapy, except possibly symptomatic therapy, is indicated. When cutaneous vasculitis persists and when there is no evidence of an inciting agent, an associated disease, or an underlying systemic vasculitis, the decision to treat should be based on weighing the balance between the degree of symptoms and the risk of treatment. Some cases of idiopathic cutaneous vasculitis resolve spontaneously, whereas others remit and relapse. In patients with persistent vasculitis, a variety of therapeutic regimens have been tried with variable results. In general, the treatment of idiopathic cutaneous vasculitis has not been satisfactory. Fortunately, since the disease is generally limited to the skin, this lack of consistent response to therapy usually does not lead to a life-threatening situation. Agents with which there have been anecdotal reports of success include dapsone, colchicine, hydroxychloroquine, and nonsteroidal anti-inflammatory agents. Glucocorticoids are often used in the treatment of idiopathic cutaneous vasculitis. T erapy is usually instituted as prednisone, 1 mg/kg per day, with rapid tapering where possible, either directly to discontinuation or by conversion to an alternate-day regimen followed by ultimate discontinuation. In cases that prove refractory to glucocorticoids, a trial of a cytotoxic agent may be indicated. Patients with chronic vasculitis isolated to cutaneous venules rarely respond dramatically to any therapeutic regimen, and cytotoxic agents should be used only as a last resort in these patients. Methotrexate and azathioprine have been used in such situations in anecdotal reports. Although cyclophosphamide is the most effective therapy for the systemic vasculitides, it should almost never be used for idiopathic cutaneous vasculitis because of the potential toxicity.

PRIMARY CENTRAL NERVOUS SYSTEM (CNS) VASCULITIS

Primary CNS vasculitis is an uncommon clinicopathologic entity characterized by vasculitis restricted to the vessels of the CNS without other apparent systemic vasculitis. T e inflammatory process is usually composed of mononuclear cell infiltrates with or without granuloma formation.

Patients may present with headaches, altered mental function, and focal neurologic defects. Systemic symptoms are generally absent. Devastating neurologic abnormalities may occur depending on the extent of vessel involvement. T e diagnosis can be suggested by

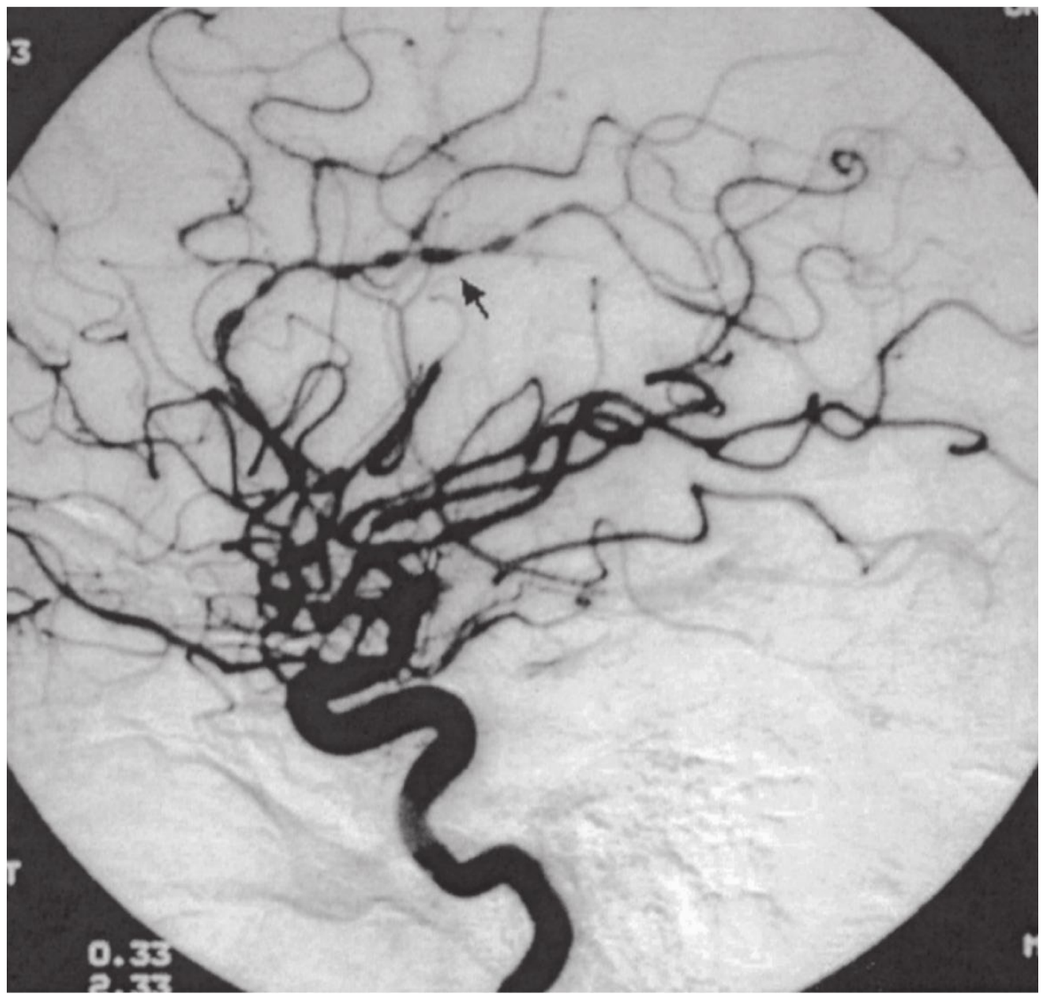


FIGURE 11-4
Cerebral arteriogram from a 32-year-old male with primary central nervous system vasculitis. Dramatic beading (arrow) typical of vasculitis is seen.

abnormal magnetic resonance imaging of the brain, an abnormal lumbar puncture, and/or demonstration of characteristic vessel abnormalities on arteriography **(Fig. 11-4)**, but it is confirmed by biopsy of the brain parenchyma and leptomeninges. In the absence of a brain biopsy, care should be taken not to misinterpret as true primary vasculitis arteriographic abnormalities that might actually be related to another cause. An important entity in the differential diagnosis is reversible cerebral vasoconstrictive syndrome, which typically presents with "thunderclap" headache and is associated with arteriographic abnormalities that mimic primary CNS vasculitis that are reversible. Other diagnostic considerations include infection, atherosclerosis, emboli, connective tissue disease, sarcoidosis, malignancy, and drug-associated causes. T e prognosis of granulomatous primary CNS vasculitis is poor; however, some reports indicate that glucocorticoid therapy, alone or together with cyclophosphamide administered as described above, has induced clinical remissions.

BEHÇET'S DISEASE

Behçet's disease is a clinicopathologic entity characterized by recurrent episodes of oral and genital ulcers, iritis, and cutaneous lesions. T e underlying pathologic process is a leukocytoclastic venulitis, although vessels of any size and in any organ can be involved **(Chap. 12)**.

COGAN'S SYNDROME

Cogan's syndrome is characterized by interstitial keratitis together with vestibuloauditory symptoms. It may be associated with a systemic vasculitis, particularly aortitis with involvement of the aortic valve. Glucocorticoids are the mainstay of treatment. Initiation of treatment as early as possible after the onset of hearing loss improves the likelihood of a favorable outcome.

KAWASAKI DISEASE

Kawasaki disease is an acute, febrile, multisystem disease of children. Some 80% of cases occur prior to the age of 5, with the peak incidence occurring at ≤2 years. It is characterized by nonsuppurative cervical adenitis and changes in the skin and mucous membranes such as edema; congested conjunctivae; erythema of the oral cavity, lips, and palms; and desquamation of the skin of the fingertips. Although the disease is generally benign and self-limited, it is associated with coronary artery aneurysms in □25% of cases, with an overall case fatality rate of 0.5–2.8%. T ese complications usually occur between the third and fourth weeks of illness during the convalescent stage. Vasculitis of the coronary arteries is seen in almost all the fatal cases that have been autopsied. T ere is typical intimal proliferation and infiltration of the vessel wall with mononuclear cells. Beadlike aneurysms and thromboses may be seen along the artery. Other manifestations include pericarditis, myocarditis, myocardial ischemia and infarction, and cardiomegaly.

Apart from the up to 2.8% of patients who develop fatal complications, the prognosis of this disease for uneventful recovery is excellent. High-dose IV γ-globulin (2 g/kg as a single infusion over 10 h) together with aspirin (100 mg/kg per day for 14 days followed by 3–5 mg/kg per day for several weeks) have been shown to be effective in reducing the prevalence of coronary artery abnormalities when administered early in the course of the disease. Surgery may be necessary for Kawasaki disease patients who have giant coronary artery aneurysms or other coronary complications. Surgical treatment most commonly includes thromboendarterectomy, thrombus clearing, aneurysmal reconstruction, and coronary artery bypass grafting.

POLYANGIITIS OVERLAP SYNDROMES

Some patients with systemic vasculitis manifest clinicopathologic characteristics that do not fit precisely into any specific disease but have overlapping features of different vasculitides. Active systemic vasculitis in such settings has the same potential for causing irreversible organ system damage as when it occurs in one of the defined syndromes listed in Table 11-1. T e diagnostic and therapeutic considerations as well as the prognosis for these patients depend on the sites and severity of active vasculitis. Patients with vasculitis that could potentially cause irreversible damage to a major organ system should be treated as described under "Granulomatosis with Polyangiitis (Wegener's)."

SECONDARY VASCULITIS

DRUG-INDUCED VASCULITIS

Vasculitis associated with drug reactions usually presents as palpable purpura that may be generalized or limited to the lower extremities or other dependent areas; however, urticarial lesions, ulcers, and hemorrhagic blisters may also occur. Signs and symptoms may be limited to the skin, although systemic manifestations such as fever, malaise, and polyarthralgias may occur. Although the skin is the predominant organ involved, systemic vasculitis may result from drug reactions. Drugs that have been implicated in vasculitis include allopurinol, thiazides, gold, sulfonamides, phenytoin, and penicillin.

An increasing number of drugs have been reported to cause vasculitis associated with antimyeloperoxidase ANCA. Of these, the best evidence of causality exists for hydralazine and propylthiouracil. T e clinical manifestations in ANCA-positive drug-induced vasculitis can range from cutaneous lesions to glomerulonephritis and pulmonary hemorrhage. Outside of drug discontinuation, treatment should be based on the severity of the vasculitis. Patients with immediately life-threatening small-vessel vasculitis should initially be treated with glucocorticoids and cyclophosphamide as described for granulomatosis with polyangiitis (Wegener's). Following clinical improvement, consideration may be given for tapering such agents along a more rapid schedule.

SERUM SICKNESS AND SERUM SICKNESS–LIKE REACTIONS

T ese reactions are characterized by the occurrence of fever, urticaria, polyarthralgias, and lymphadenopathy 7–10 days after primary exposure and 2–4 days after secondary exposure to a heterologous protein (classic serum sickness) or a nonprotein drug such as penicillin or sulfa (serum sickness–like reaction). Most of the manifestations are not due to a vasculitis; however, occasional patients will have typical cutaneous venulitis that may progress rarely to a systemic vasculitis.

VASCULITIS ASSOCIATED WITH OTHER UNDERLYING DISEASES

Certain infections may directly trigger an inflammatory vasculitic process. For example, rickettsias can invade and proliferate in the endothelial cells of small blood vessels causing a vasculitis. In addition, the inflammatory response around blood vessels associated with certain systemic fungal diseases such as histoplasmosis may mimic a primary vasculitic process. A leukocytoclastic vasculitis predominantly involving the skin with occasional involvement of other organ systems may be a minor component of many other infections. T ese include subacute bacterial endocarditis, Epstein-Barr virus infection, HIV infection, and a number of other infections.

Vasculitis can be associated with certain malignancies, particularly lymphoid or reticuloendothelial neoplasms. Leukocytoclastic venulitis confined to the skin is the most common finding; however, widespread systemic vasculitis may occur. Of particular note is the association of hairy cell leukemia with polyarteritis nodosa.

A number of connective tissue diseases have vasculitis as a secondary manifestation of the underlying primary process. Foremost among these are systemic lupus erythematosus **(Chap. 4)**, rheumatoid arthritis **(Chap. 6)**, inflammatory myositis **(Chap. 17)**, relapsing polychondritis **(Chap. 13)**, and Sjögren's syndrome **(Chap. 9)**. The most common form of vasculitis in these conditions is the small-vessel venulitis isolated to the skin. However, certain patients may develop a fulminant systemic necrotizing vasculitis.

Secondary vasculitis has also been observed in association with ulcerative colitis, congenital deficiencies of various complement components, sarcoidosis, primary biliary cirrhosis, α_1-antitrypsin deficiency, and intestinal bypass surgery.

CHAPTER 12

BEHÇET'S SYNDROME

Haralampos M. Moutsopoulos

DEFINITION, INCIDENCE, AND PREVALENCE

Behçet's syndrome is a multisystem disorder presenting with recurrent oral and genital ulcerations as well as ocular involvement. The diagnosis is clinical and based on internationally agreed diagnostic criteria **(Table 12-1)**.

The syndrome affects young males and females from the Mediterranean region, the Middle East, and the Far East, suggesting a link with the ancient Silk Route. Males and females are affected equally, but males often have more severe disease. Blacks are very infrequently affected.

PATHOGENESIS

The etiology and pathogenesis of this syndrome remain obscure. The disease appears to be in the crossroads of autoinflammatory and autoimmune disorders. The main pathologic lesion is systemic perivasculitis with early neutrophil infiltration and endothelial swelling. In some patients, diffuse inflammatory disease, involving all layers of large vessels and resulting to formation of pseudoaneurysms, suggests vasculitis of vasa vasorum. Apart from activated neutrophils, increased numbers of infiltrating T_H1, T_H17, cytotoxic CD8+, and γδ T cells are observed, suggesting a link between innate and adaptive autoreactive immune response. Circulating autoantibodies against α-enolase of endothelial cells, selenium binding protein, and anti-Saccharomyces cerevisiae antibodies have been observed, but their pathogenic role remains unclear. A recent genome-wide association study confirmed the known association of Behçet's syndrome with HLA-B*51 and identified a second, independent association within the major histocompatibility complex (MHC) class I region. In addition, an association with interleukin (IL) 10 and the IL-23R–IL-12RB2 locus was also observed. Interestingly, the disease-associated IL-10 variant was correlated with diminished mRNA expression and low protein production.

CLINICAL FEATURES

The recurrent aphthous ulcerations are a sine qua non for the diagnosis. The ulcers are usually painful, are shallow or deep with a central yellowish necrotic base, appear singly or in crops, and are located anywhere in the oral cavity. Small ulcers, less than 10 mm in diameter, are seen in 85% of patients, whereas large or herpetiform lesions are less frequent. The ulcers persist for 1–2 weeks and subside without leaving scars. The genital ulcers are less common but more specific, are painful, do not affect the glans penis or urethra, and produce scrotal scars.

Skin involvement is observed in 80% of patients and includes folliculitis, erythema nodosum, an acne-like exanthem, and, infrequently, vasculitis, Sweet syndrome, and pyoderma gangrenosum. Nonspecific skin inflammatory reactivity to any scratches or intradermal saline injection (pathergy test) is a common and specific manifestation.

Eye involvement with scarring and bilateral panuveitis is the most dreaded complication, since it occasionally progresses rapidly to blindness. The eye disease, occurring in 50% of patients, is usually present at the onset but may also develop within the first few years. In addition to iritis, posterior uveitis, retinal vessel occlusions, and optic neuritis can be seen in some patients with the syndrome.

Nondeforming arthritis or arthralgias are seen in 50% of patients and affect the knees and ankles.

Superficial or deep peripheral vein thrombosis is seen in 30% of patients. Pulmonary emboli are a rare complication. The superior vena cava is obstructed occasionally, producing a dramatic clinical picture. Arterial involvement occurs in less than 5% of patients

TABLE 12-1

DIAGNOSTIC CRITERIA OF BEHÇET'S SYNDROME

Recurrent oral ulceration plus two of the following:
- Recurrent genital ulceration
- Eye lesions
- Skin lesions
- Pathergy test

and presents with aortitis or peripheral arterial aneurysm and arterial thrombosis. Pulmonary artery vasculitis presenting with dyspnea, cough, chest pain, hemoptysis, and infiltrates on chest roentgenograms has been reported in 5% of patients and should be differentiated from thromboembolic disease since it warrants anti-inflammatory and not thrombolytic therapy.

Neurologic involvement (5–10%) appears mainly in the parenchymal form (80%); it is associated with brainstem involvement and has a serious prognosis (central nervous system [CNS]-Behçet's syndrome). IL-6 is persistently raised in cerebrospinal fluid of these patients. Cerebral venous thrombosis is most frequently observed in the superior sagittal and transverse sinuses and is associated with headache and increased intracranial pressure. Magnetic resonance imaging (MRI) and/or proton magnetic resonance spectroscopy (MRS) are very sensitive and should be employed if CNS-Behçet's syndrome is suspected.

Gastrointestinal involvement is seen more frequently in patients from Japan and consists of mucosal ulcerations of the gut, resembling Crohn's disease.

Epididymitis is seen in 5% of patients, whereas amyloidosis of AA type and glomerulonephritis are uncommon.

Laboratory findings are mainly nonspecific indices of inflammation, such as leukocytosis and elevated erythrocyte sedimentation rate, as well as C-reactive protein levels.

TREATMENT Behçet's Syndrome

The severity of the syndrome usually abates with time. Apart from the patients with CNS-Behçet's syndrome and major vessel disease, the life expectancy seems to be normal and the only serious complication is blindness.

Mucous membrane involvement may respond to topical glucocorticoids in the form of mouthwash or paste. In more serious cases, thalidomide (100 mg/d) is effective. Thrombophlebitis is treated with aspirin, 325 mg/d. Colchicine can be beneficial for the mucocutaneous manifestations and arthritis. Uveitis and CNS-Behçet's syndrome require systemic glucocorticoid therapy (prednisone, 1 mg/kg per day) and azathioprine (2–3 mg/kg per day). Cyclosporine (5 mg/kg) has been used for sight-threatening uveitis, alone or in combination with azathioprine. Pulse doses of cyclophosphamide are useful early in the course of the disease for pulmonary or peripheral arterial aneurysms. Anti–tumor necrosis factor therapy is recommended in panuveitis refractory to immunosuppressives. Administration of this therapy improves visual acuity in more than two-thirds of patients. There has been recent data with the use of the oral phosphodiesterase-4 inhibitor ampremilast in Behcet's syndrome. Although the results were encouraging, this was a short-term study focusing on the oral ulcer manifestation such that greater experience is needed in order to understand whether this agent may be effcacious.

CHAPTER 13

RELAPSING POLYCHONDRITIS

Carol A. Langford

Relapsing polychondritis is an uncommon disorder of unknown cause characterized by inflammation of cartilage predominantly affecting the ears, nose, and laryngotracheobronchial tree. Other manifestations include scleritis, neurosensory hearing loss, polyarthritis, cardiac abnormalities, skin lesions, and glomerulonephritis. Relapsing polychondritis has been estimated to have an incidence of 3.5 per million population per year. T e peak age of onset is between the ages of 40 and 50 years, but relapsing polychondritis may affect children and the elderly. It is found in all races, and both sexes are equally affected. No familial tendency is apparent. A significantly higher frequency of HLA-DR4 has been found in patients with relapsing polychondritis than in healthy individuals. A predominant subtype allele(s) of HLA-DR4 was not found. Approximately 30% of patients with relapsing polychondritis will have another rheumatologic disorder, the most frequent being systemic vasculitis, followed by rheumatoid arthritis, and systemic lupus erythematosus (SLE). Nonrheumatic disorders associated with relapsing polychondritis include Hashimoto's thyroiditis, primary biliary cirrhosis, and myelodysplastic syndrome **(Table 13-1)**. In most cases, these disorders antedate the appearance of relapsing polychondritis, usually by months or years; however, in other instances, the onset of relapsing polychondritis can accompany disease presentation.

PATHOLOGY AND PATHOPHYSIOLOGY

T e earliest abnormality of hyaline and elastic cartilage noted histologically is a focal or diffuse loss of basophilic staining indicating depletion of proteoglycan from the cartilage matrix. Inflammatory infiltrates are found adjacent to involved cartilage and consist predominantly of mononuclear cells and occasional plasma cells. In acute disease, polymorphonuclear white cells may also be present. Destruction of cartilage begins at the outer edges and advances centrally. T ere is lacunar breakdown and loss of chondrocytes. Degenerating cartilage is replaced by granulation tissue and later by fibrosis and focal areas of calcification. Small loci of cartilage regeneration may be present. Immunofluorescence studies have shown immunoglobulins and complement at sites of involvement. Extracellular granular material observed in the degenerating cartilage matrix by electron microscopy has been interpreted to be enzymes, immunoglobulins, or proteoglycans.

Immunologic mechanisms play a role in the pathogenesis of relapsing polychondritis. T e accumulating data strongly suggest that both humoral and cell-mediated immunity play an important role in the pathogenesis of relapsing polychondritis. Immunoglobulin and complement deposits are found at sites of inflammation. In addition, antibodies to type II collagen and to matrilin-1 and immunecomplexes are detected in the sera of some patients. T e possibility that an immune response to type II collagen may be important in the pathogenesis is supported experimentally by the occurrence of auricular chondritis in rats immunized with type II collagen. Antibodies to type II collagen are found in the sera of these animals, and immune deposits are detected at sites of ear inflammation. Humoral immune responses to type IX and type XI collagen, matrilin-1, and cartilage oligomeric matrix protein have been demonstrated in some patients. In a study, rats immunized with matrilin-1 were found to develop severe inspiratory stridor and swelling of the nasal septum. T e rats had severe inflammation with erosions of the involved cartilage, which was characterized by increased numbers of CD4+ and CD8+ T cells in the lesions. T e cartilage of the joints and ear pinna was not involved. All had IgG antibodies to matrilin-1. Matrilin-1 is a noncollagenous protein present in the extracellular matrix in cartilage. It is present in high concentrations in the trachea and is also present in the

TABLE 13-1

DISORDERS ASSOCIATED WITH RELAPSING POLYCHONDRITIS[a]

Systemic vasculitis
Rheumatoid arthritis
Systemic lupus erythematosus
Overlapping connective tissue disease
Spondyloarthritides
Behçet's disease
Polymyalgia rheumatica
Primary biliary cirrhosis
Pulmonary fibrosis
Hashimoto's thyroiditis
Myelodysplastic syndrome

[a]Systemic vasculitis is the most common association, followed by rheumatoid arthritis and systemic lupus erythematosus.
Source: Modified from CJ Michet et al: Ann Intern Med 104:74, 1986.

nasal septum but not in articular cartilage. A subsequent study demonstrated serum anti-matrilin-1 antibodies in approximately 13% of patients with relapsing polychondritis; approximately 70% of these patients had respiratory symptoms. Cell-mediated immunity may also be operative in causing tissue injury, since lymphocyte transformation can be demonstrated when lymphocytes of patients are exposed to cartilage extracts. T cells specific for type II collagen have been found in some patients, and CD4+ T cells have been observed at sites of cartilage inflammation.

CLINICAL MANIFESTATIONS

The onset of relapsing polychondritis is frequently abrupt, with the appearance of one or two sites of cartilaginous inflammation. The pattern of cartilaginous involvement and the frequency of episodes vary widely among patients. Noncartilaginous presentations may also occur. Systemic inflammatory features such as fever, fatigue, and weight loss occur and may precede the clinical signs of relapsing polychondritis by several weeks. Relapsing polychondritis may go unrecognized for several months or even years in patients who only initially manifest intermittent joint pain and/or swelling, or who have unexplained eye inflammation, hearing loss, valvular heart disease, or pulmonary symptoms.

Auricular chondritis is the most frequent presenting manifestation of relapsing polychondritis, occurring in 40% of patients and eventually affecting about 85% of patients **(Table 13-2)**. One or both ears are involved, either sequentially or simultaneously. Patients experience the sudden onset of pain, tenderness, and swelling of the cartilaginous portion of the ear **(Fig. 13-1)**. It is typically involves the pinna of the ears,

TABLE 13-2

CLINICAL MANIFESTATIONS OF RELAPSING POLYCHONDRITIS

CLINICAL FEATURE	PRESENTING	CUMULATIVE
	Frequency, %	
Auricular chondritis	43	89
Arthritis	32	72
Nasal chondritis	21	61
Ocular inflammation	18	59
Laryngotracheal symptoms	23	55
Reduced hearing	7	40
Saddle nose deformity	11	25
Cutaneous	4	25
Laryngotracheal stricture	15	23
Vasculitis	2	14
Elevated creatinine	7	13
Aortic or mitral regurgitation	0	12

Source: Modified from PD Kent et al: Curr Opin Rheumatol 16:56, 2004.

sparing the earlobes because they do not contain cartilage. The overlying skin has a beefy red or violaceous color. Prolonged or recurrent episodes lead to cartilage destruction and result in a flabby or droopy ear. Swelling may close off the eustachian tube or the external auditory meatus, either of which can impair hearing.

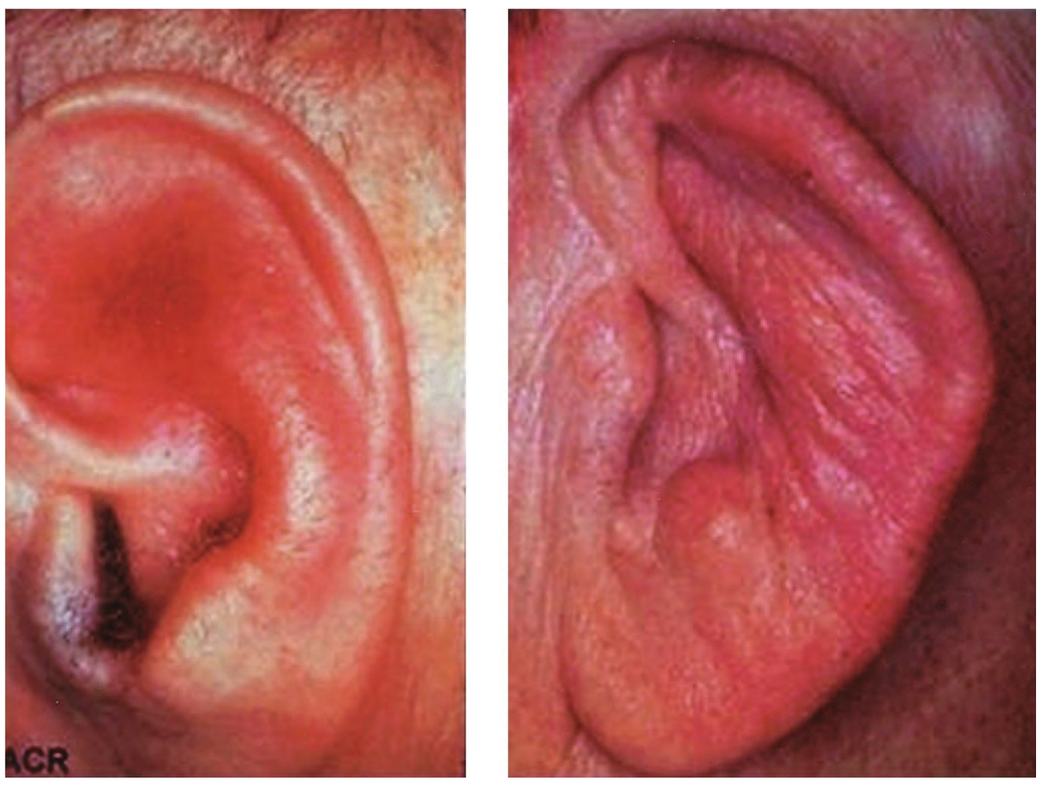


FIGURE 13-1
Left. The pinna is erythematous, swollen, and tender. Not shown is the ear lobule that is spared as there is no underlying cartilage. Right. The pinna is thickened and deformed. The destruction of the underlying cartilage results in a floppy ear. (Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, ©1991, 1995, 1997, 1998, 1999. Used by permission of the American College of Rheumatology.)

Inflammation of the internal auditory artery or its cochlear branch produces hearing loss, vertigo, ataxia, nausea, and vomiting. Vertigo is almost always accompanied by hearing loss.

Approximately 61% of patients will develop nasal involvement, with 21% having this at the time of presentation. Patients may experience nasal stuffiness, rhinorrhea, and epistaxis. T e bridge of the nose and surrounding tissue become red, swollen, and tender and may collapse, producing a saddle nose deformity **(Fig. 13-2)**. In some patients, nasal deformity develops insidiously without overt inflammation. Saddle nose is observed more frequently in younger patients, especially in women.

Joint involvement is the presenting manifestation in relapsing polychondritis in approximately one-third of patients and may be present for several months before other features appear. Eventually, more than one-half of the patients will have arthralgias or arthritis. T e arthritis is usually asymmetric and oligo- or polyarticular, and it involves both large and small peripheral joints. An episode of arthritis lasts from a few days to several weeks and resolves spontaneously without joint erosion or deformity. Attacks of arthritis may not be temporally related to other manifestations of relapsing polychondritis. Joint fluid has been reported to be noninflammatory. In addition to peripheral joints, inflammation may involve the costochondral, sternomanubrial, and sternoclavicular cartilages. Destruction of these cartilages may result in a pectus excavatum deformity or even a flail anterior chest wall.



FIGURE 13-2
Saddle nose results from destruction and collapse of the nasal cartilage. (Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, ©1991, 1995, 1997, 1998, 1999. Used by permission of the American College of Rheumatology.)

Eye manifestations occur in more than one-half of patients and include conjunctivitis, episcleritis, scleritis, iritis, uveitis, and keratitis. Ocular inflammation can be severe and visually threatening. Other manifestations include eyelid and periorbital edema, proptosis, optic neuritis, extraocular muscle palsies, retinal vasculitis, and renal vein occlusion.

Laryngotracheobronchial involvement occurs in □50% of patients and is among the most serious manifestations of relapsing polychondritis. Symptoms include hoarseness, a nonproductive cough, and tenderness over the larynx and proximal trachea. Mucosal edema, strictures, and/or collapse of laryngeal or tracheal cartilage may cause stridor and life-threatening airway obstruction necessitating tracheostomy. Involvement can extend into the lower airways resulting in tracheobronchomalacia. Collapse of cartilage in bronchi leads to pneumonia and, when extensive, to respiratory insufficiency.

Cardiac valvular regurgitation occurs in about 5–10% of patients and is due to progressive dilation of the valvular ring or to destruction of the valve cusps. Aortic regurgitation occurs in about 7% of patients, with the mitral and other heart valves being affected less of en. Other cardiac manifestations include pericarditis, myocarditis, coronary vasculitis, and conduction abnormalities. Aneurysms of the proximal, thoracic, or abdominal aorta may occur even in the absence of active chondritis and occasionally rupture.

Renal disease occurs in about 10% of patients. T e most common renal lesions include mesangial expansion or segmental necrotizing glomerulonephritis, which have been reported to have small amounts of electron-dense deposits in the mesangium where there is also faint deposition of C3 and/or IgG or IgM. Tubulointerstitial disease and IgA nephropathy have also been reported.

Approximately 25% of patients have skin lesions, which can include purpura, erythema nodosum, erythema multiforme, angioedema/urticaria, livedo reticularis, and panniculitis.

Features of vasculitis are seen in up to 25% of patients and can affect any size vessel. Large vessel vasculitis may present with aortic aneurysms, and medium vessel disease may affect the coronary, hepatic, mesenteric, or renal arteries or vessel supplying nerves. Skin vessel disease and involvement of the postcapillary venules can also occur. A variety of primary vasculitides have also been reported to occur in association with relapsing polychondritis **(Chap. 11)**. One specific overlap is the "MAGIC" syndrome (mouth and genital ulcers with inflamed cartilage) in which patients present with features of both relapsing polychondritis and Behçet's disease **(Chap. 12)**.

LABORATORY FINDINGS AND DIAGNOSTIC IMAGING

There are no laboratory features that are diagnostic for relapsing polychondritis. Mild leukocytosis and normocytic, normochromic anemia are often present. Eosinophilia is observed in 10% of patients. The erythrocyte sedimentation rate and C-reactive protein are usually elevated. Rheumatoid factor and antinuclear antibody tests are occasionally positive in low titers, and complement levels are normal. Antibodies to type II collagen are present in fewer than one-half of the patients and are not specific. Circulating immune complexes may be detected, especially in patients with early active disease. Elevated levels of γ globulin may be present. Antineutrophil cytoplasmic antibodies (ANCA), either cytoplasmic (cANCA) or perinuclear (pANCA), are found in some patients with active disease. However, on target antigen–specific testing, there are only occasional reports of positive myeloperoxidase-ANCA, and proteinase 3-ANCA are very rarely found in relapsing polychondritis.

The upper and lower airways can be evaluated by imaging techniques such as computed tomography and magnetic resonance imaging (MRI). Bronchoscopy provides direct visualization of the airways but can be a high-risk procedure in patients with airway compromise. Pulmonary function testing with flow-volume loops can show inspiratory and/or expiratory obstruction. Imaging can also be useful to detect extracartilaginous disease. The chest film may show widening of the ascending or descending aorta due to an aneurysm, and cardiomegaly when aortic insufficiency is present. MRI can assess aortic aneurysmal dilatation. Electrocardiography and echocardiography can be useful in further evaluating for cardiac features of disease.

DIAGNOSIS

Diagnosis is based on recognition of the typical clinical features. Biopsies of the involved cartilage from the ear, nose, or respiratory tract will confirm the diagnosis but are only necessary when clinical features are not typical. Diagnostic criteria were suggested in 1976 by McAdam et al and modified by Damiani and Levine in 1979. These criteria continue to be generally used in clinical practice. McAdam et al proposed the following: (1) recurrent chondritis of both auricles; (2) nonerosive inflammatory arthritis; (3) chondritis of nasal cartilage; (4) inflammation of ocular structures, including conjunctivitis, keratitis, scleritis/episcleritis, and/or uveitis; (5) chondritis of the laryngeal and/or tracheal cartilages; and (6) cochlear and/or vestibular damage manifested by neurosensory hearing loss, tinnitus, and/or vertigo. The diagnosis is certain when three or more of these features are present along with a positive biopsy from the ear, nasal, or respiratory cartilage. Damiani and Levine later suggested that the diagnosis could be made when one or more of the above features and a positive biopsy were present, when two or more separate sites of cartilage inflammation were present that responded to glucocorticoids or dapsone, or when three or more of the above features were present.

The differential diagnosis of relapsing polychondritis is centered around its sites of clinical involvement. Patients with granulomatosis with polyangiitis (Wegener's) may have a saddle nose and tracheal involvement but can be distinguished by the primary inflammation occurring in the mucosa at these sites, the absence of auricular involvement, and the presence of pulmonary parenchymal disease. Patients with Cogan's syndrome have interstitial keratitis and vestibular and auditory abnormalities, but this syndrome does not involve the respiratory tract or ears. Reactive arthritis may initially resemble relapsing polychondritis because of oligoarticular arthritis and eye involvement, but it is distinguished in time by the appearance of urethritis and typical mucocutaneous lesions and the absence of nose or ear cartilage involvement. Rheumatoid arthritis may initially suggest relapsing polychondritis because of arthritis and eye inflammation. The arthritis in rheumatoid arthritis, however, is erosive and symmetric. In addition, rheumatoid factor titers are usually high compared with those in relapsing polychondritis, and anticyclic citrullinated peptide is usually not seen. Bacterial infection of the pinna may be mistaken for relapsing polychondritis but differs by usually involving only one ear, including the earlobe. Auricular cartilage may also be damaged by trauma or frostbite. Nasal destructive disease and auricular abnormalities can also be seen in patients using cocaine adulterated with levamisole. Ear involvement in this setting differs from relapsing polychondritis by typically manifesting as purpuric plaques with necrosis extending to the pinna, which does not contain cartilage.

TREATMENT Relapsing Polychondritis

In patients with active chondritis, prednisone, 40–60 mg/d, is often effective in suppressing disease activity; it is tapered gradually once disease is controlled. In some patients, prednisone can be stopped, whereas in others, low doses in the range of 5–10 mg/d are required for continued suppression of disease. Dapsone 50–100 mg/d has been effective for cartilage inflammation and joint features in some patients. Other immunosuppressive drugs such as cyclophosphamide, methotrexate, azathioprine, or cyclosporine should be reserved for patients who have severe organ-threatening disease, fail to respond to prednisone, or require high doses to control disease activity. Patients with significant ocular inflammation

of en require intraocular glucocorticoids as well as high doses of prednisone. T ere are a small number of reports on the use of tumor necrosis factor antagonists, rituximab (anti-CD20), and tocilizumab (anti-interleukin 6 receptor), which are too few in number to assess efficacy. Heart valve replacement or repair of an aortic aneurysm may be necessary. When airway obstruction is severe, tracheostomy is required. Stents may be necessary in patients with tracheobronchial collapse.

PATIENT OUTCOME, PROGNOSIS, AND SURVIVAL

T e course of relapsing polychondritis is highly variable. Some patients experience inflammatory episodes lasting from a few days to several weeks that then subside spontaneously or with treatment. Attacks may recur at intervals varying from weeks to months. In other patients, the disease has a chronic, smoldering course that may be severe. In one study, the 5-year estimated survival rate was 74% and the 10-year survival rate was 55%. In contrast to earlier series, only about one-half of the deaths could be attributed to relapsing polychondritis or complications of treatment. Airway complications accounted for only 10% of all fatalities. In general, patients with more widespread disease have a worse prognosis.

Acknowledgment

T is chapter represents a revised version of the text authored by Dr. Bruce C. Gilliland that appeared in previous editions of Harrison's Principles of Internal Medicine. Dr. Gilliland passed away on February 17, 2007, and had been a contributor to Harrison's since the 11th edition.

CHAPTER 14

SARCOIDOSIS

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DEFINITION

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas. T e disease is often multisystem and requires the presence of involvement in two or more organs for a specific diagnosis. T e finding of granulomas is not specific for sarcoidosis, and other conditions known to cause granulomas must be ruled out. T ese conditions include mycobacterial and fungal infections, malignancy, and environmental agents such as beryllium. Although sarcoidosis can affect virtually every organ of the body, the lung is most commonly affected. Other organs commonly affected are the liver, skin, and eye. T e clinical outcome of sarcoidosis varies, with remission occurring in over one-half of patients within a few years of diagnosis; however, the remaining patients may develop a chronic disease that lasts for decades.

ETIOLOGY

Despite multiple investigations, the cause of sarcoidosis remains unknown. Currently, the most likely etiology is an infectious or noninfectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Among the possible infectious agents, careful studies have shown a much higher incidence of Propionibacter acnes in the lymph nodes of sarcoidosis patients compared to controls. An animal model has shown that P. acnes can induce a granulomatous response in mice similar to sarcoidosis. Others have demonstrated the presence of a mycobacterial protein (Mycobacterium tuberculosis catalase-peroxidase [mKatG]) in the granulomas of some sarcoidosis patients. T is protein is very resistant to degradation and may represent the persistent antigen in sarcoidosis. Immune response to this and other mycobacterial proteins has been documented by another laboratory. T ese studies suggest that a mycobacterium similar to M. tuberculosis could be responsible for sarcoidosis. T e mechanism exposure/infection with such agents has been the focus of other studies. Environmental exposures to insecticides and mold have been associated with an increased risk for disease. In addition, health care workers appear to have an increased risk. Also, sarcoidosis in a donor organ has occurred after transplantation into a sarcoidosis patient. Some authors have suggested that sarcoidosis is not due to a single agent but represents a particular host response to multiple agents. Some studies have been able to correlate the environmental exposures to genetic markers. T ese studies have supported the hypothesis that a genetically susceptible host is a key factor in the disease.

INCIDENCE, PREVALENCE, AND GLOBAL IMPACT



Sarcoidosis is seen worldwide, with the highest prevalence reported in the Nordic population. In the United States, the disease has been reported more commonly in African Americans than whites, with the ratio of African Americans to whites ranging from 3:1 to 17:0. Women appear to be slightly more susceptible than men. T e higher incidence in African Americans may have been influenced by the fact that African Americans seem to develop more extensive and chronic pulmonary disease. Because most sarcoidosis clinics are run by pulmonologists, a selection bias may have occurred. Worldwide, the prevalence of the disease varies from 20–60 per 100,000 for many groups such as Japanese, Italians, and American whites. Higher rates occur in Ireland and Nordic countries. In one closely observed community in Sweden, the lifetime risk for developing sarcoidosis was 3%.

Sarcoidosis often occurs in young, otherwise healthy adults. It is uncommon to diagnose the disease in someone under age 18. However, it has become clear that a second peak in incidence develops around age 60. In a study of >700 newly diagnosed sarcoidosis patients in the United States, one-half of the patients were ≥40 years at the time of diagnosis.

Although most cases of sarcoidosis are sporadic, a familial form of the disease exists. At least 5% of patients with sarcoidosis will have a family member with sarcoidosis. Sarcoidosis patients who are Irish or African American seem to have a two to three times higher rate of familial disease.

PATHOPHYSIOLOGY AND IMMUNOPATHOGENESIS

T e granuloma is the pathologic hallmark of sarcoidosis. A distinct feature of sarcoidosis is the local accumulation of inflammatory cells. Extensive studies in the lung using bronchoalveolar lavage (BAL) have demonstrated that the initial inflammatory response is an influx of T helper cells. In addition, there is an accumulation of activated monocytes. **Figure 14-1** is a proposed model for sarcoidosis. Using the HLA-CD4 complex, antigen-presenting cells present an unknown antigen to the helper T cell. Studies have clarified that specific HLA haplotypes such as HLA-DRB1*1101 are associated with an increased risk for developing sarcoidosis. In addition, different HLA haplotypes are associated with different clinical outcomes.

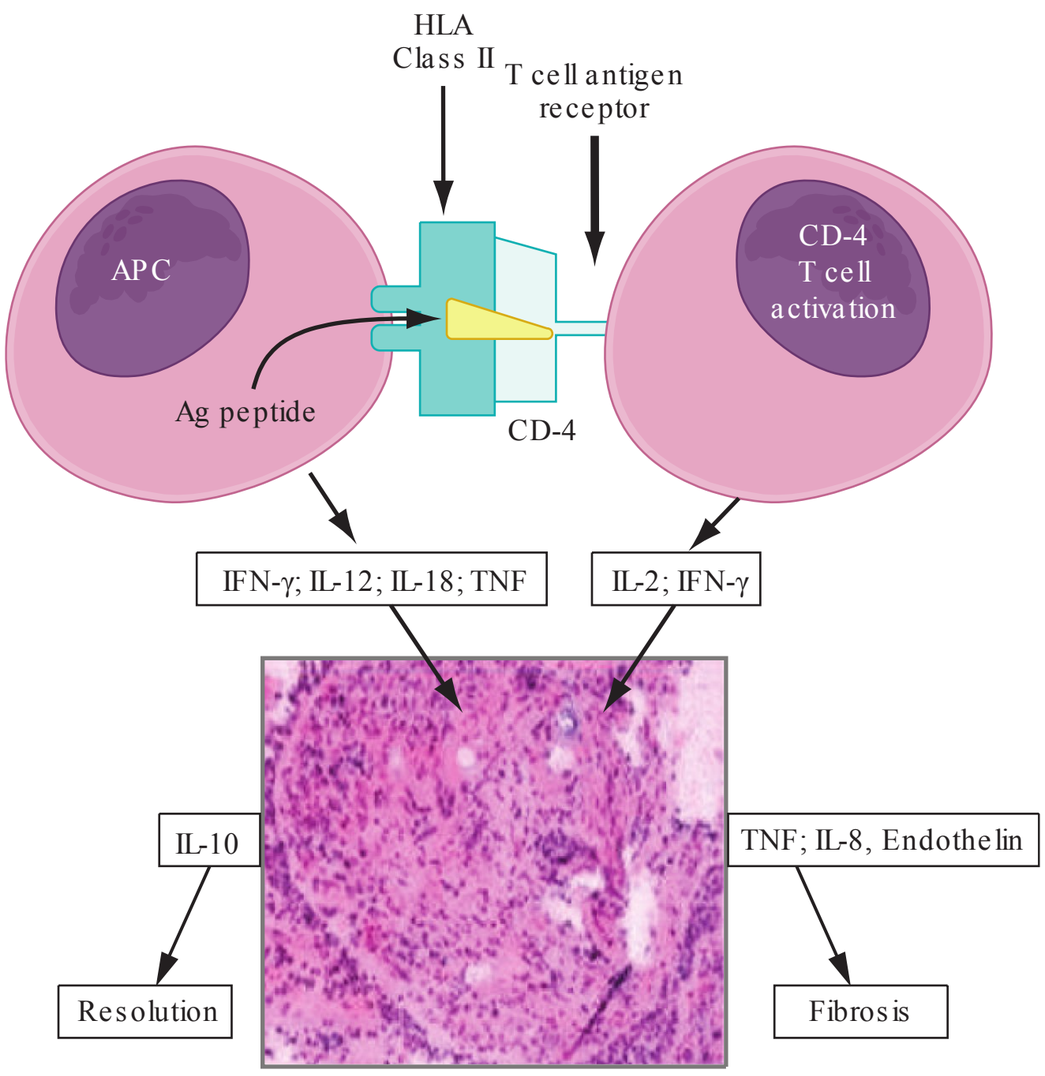


FIGURE 14-1
Schematic representation of initial events of sarcoidosis. The antigen-presenting cell and helper T cell complex leads to the release of multiple cytokines. This forms a granuloma. Over time, the granuloma may resolve or lead to chronic disease, including fibrosis. APC, antigen-presenting cell; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

T e macrophage/helper T cell cluster leads to activation with the increased release of several cytokines. T ese include interleukin (IL)-2 released from the T cell and interferon γ and tumor necrosis factor (TNF) released by the macrophage. T e T cell is a necessary part of the initial inflammatory response. In advanced, untreated HIV infection, patients who lack helper T cells rarely develop sarcoidosis. In contrast, several reports confirm that sarcoidosis becomes unmasked as HIV-infected individuals receive antiretroviral therapy, with subsequent restoration of their immune system. In contrast, treatment of established pulmonary sarcoidosis with cyclosporine, a drug that downregulates helper T cell responses, seems to have little impact on sarcoidosis.

T e granulomatous response of sarcoidosis can resolve with or without therapy. However, in at least 20% of patients with sarcoidosis, a chronic form of the disease develops. T is persistent form of the disease is associated with the secretion of high levels of IL-8. Also, studies have reported that patients with this chronic form of disease release excessive amounts of TNF in areas of inflammation. Specific gene signatures have been associated with more severe disease, such as cardiac, neurologic, and fibrotic pulmonary disease.

At diagnosis the natural history of the disease may be dif cult to predict. One form of the disease, Löfgren's syndrome, consists of erythema nodosum and hilar adenopathy on chest roentgenogram. In some cases, periarticular arthritis may be identified without erythema nodosum. Löfgren's syndrome is associated with a good prognosis, with >90% of patients experiencing disease resolution within 2 years. Recent studies have demonstrated that the HLA-DRB1*03 was found in two-thirds of Scandinavian patients with Löfgren's syndrome. More than 95% of those patients who were HLA-DRB1*03 positive had resolution of their disease within 2 years, whereas nearly one-half of the remaining patients had disease for more than 2 years. It remains to be determined whether these observations can be applied to a non-Scandinavian population.

CLINICAL MANIFESTATIONS

T e presentation of sarcoidosis ranges from patients who are asymptomatic to those with organ failure. It is unclear how often sarcoidosis is asymptomatic. In

countries where routine chest roentgenogram screening is performed, 20–30% of pulmonary cases are detected in asymptomatic individuals. T e inability to screen for other asymptomatic forms of the disease would suggest that as many as one-third of sarcoidosis patients are asymptomatic.

Respiratory complaints including cough and dyspnea are the most common presenting symptoms. In many cases, the patient presents with a 2- to 4-week history of these symptoms. Unfortunately, due to the nonspecific nature of pulmonary symptoms, the patient may see physicians for up to a year before a diagnosis is confirmed. For these patients, the diagnosis of sarcoidosis is usually only suggested when a chest roentgenogram is performed.

Symptoms related to cutaneous and ocular disease are the next two most common complaints. Skin lesions are often nonspecific. However, because these lesions are readily observed, the patient and treating physician are often led to a diagnosis. In contrast to patients with pulmonary disease, patients with cutaneous lesions are more likely to be diagnosed within 6 months of symptoms.

Nonspecific constitutional symptoms include fatigue, fever, night sweats, and weight loss. Fatigue is perhaps the most common constitutional symptom that affects these patients. Given its insidious nature, patients are usually not aware of the association with their sarcoidosis until their disease resolves.

T e overall incidence of sarcoidosis at the time of diagnosis and eventual common organ involvement are summarized in **Table 14-1**. Over time, skin, eye, and neurologic involvement seem more apparent. In the United States, the frequency of specific organ involvement appears to be affected by age, race, and gender. For example, eye disease is more common among African Americans. Under the age of 40, it occurs more frequently in women. However, in those diagnosed over the age of 40, eye disease is more common in men.

TABLE 14-1

FREQUENCY OF COMMON ORGAN INVOLVEMENT AND LIFETIME RISK[a]

	PRESENTATION, %[b]	FOLLOW-UP, %[c]
Lung	95	94
Skin	24	43
Eye	12	29
Extrathoracic lymph node	15	16
Liver	12	14
Spleen	7	8
Neurologic	5	16
Cardiac	2	3

[a]Patients could have more than one organ involved.
[b]From ACCESS study of 736 patients evaluated within 6 months of diagnosis.
[c]From follow-up of 1024 sarcoidosis patients seen at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis Clinic from 2002–2006.

LUNG

Lung involvement occurs in >90% of sarcoidosis patients. T e most commonly used method for detecting lung disease is still the chest roentgenogram. **Figure 14-2** illustrates the chest roentgenogram from a sarcoidosis patient with bilateral hilar adenopathy. Although the computed tomography (CT) scan has changed the diagnostic approach to interstitial lung disease, the CT scan is not usually considered a monitoring tool for patients with sarcoidosis. **Figure 14-3** demonstrates some of the characteristic CT features, including peribronchial thickening and reticular nodular changes, which are predominantly subpleural. T e peribronchial thickening seen on CT scan seems to explain the high yield of granulomas from bronchial biopsies performed for diagnosis.

Although the CT scan is more sensitive, the standard scoring system described by Scadding in 1961 for chest roentgenograms remains the preferred method of characterizing the chest involvement. Stage 1 is hilar adenopathy alone (Fig. 14-2), often with right paratracheal involvement. Stage 2 is a combination of adenopathy plus infiltrates, whereas stage 3 reveals infiltrates alone. Stage 4 consists of fibrosis. Usually the infiltrates in sarcoidosis are predominantly an upper lobe process. Only in a few noninfectious diseases is an upper lobe predominance noted. In addition to sarcoidosis,

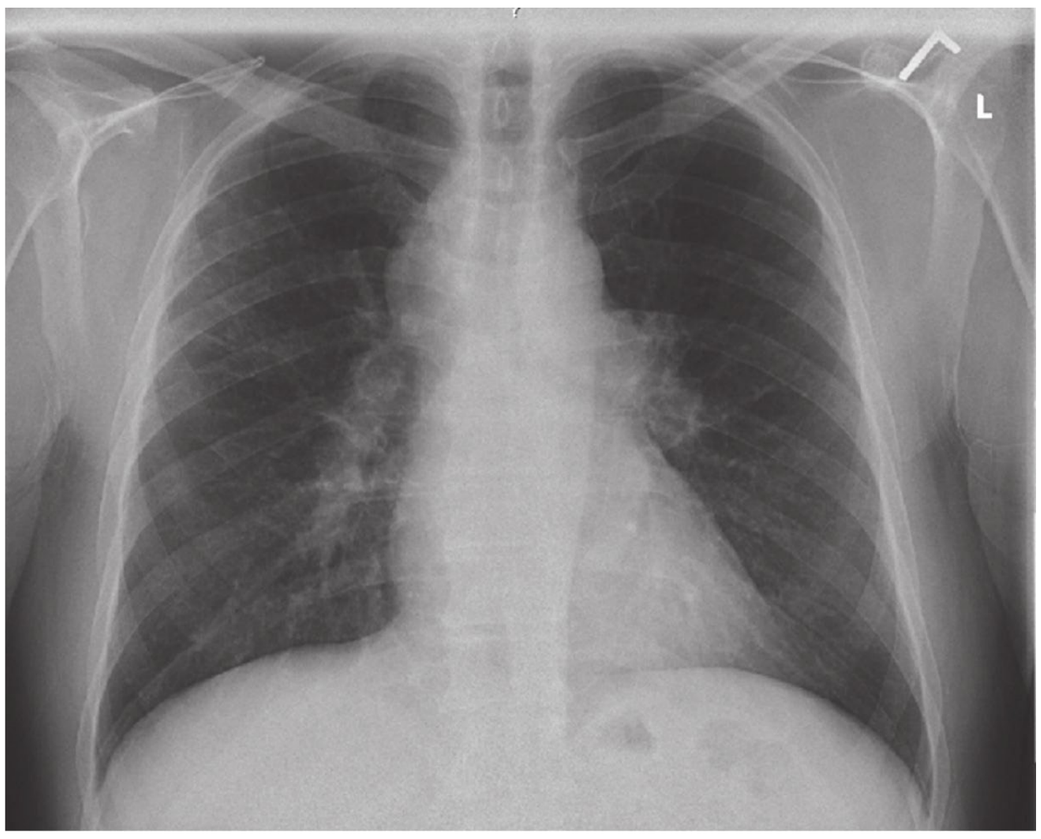


FIGURE 14-2
Posterior-anterior chest roentgenogram demonstrating bilateral hilar adenopathy, stage 1 disease.

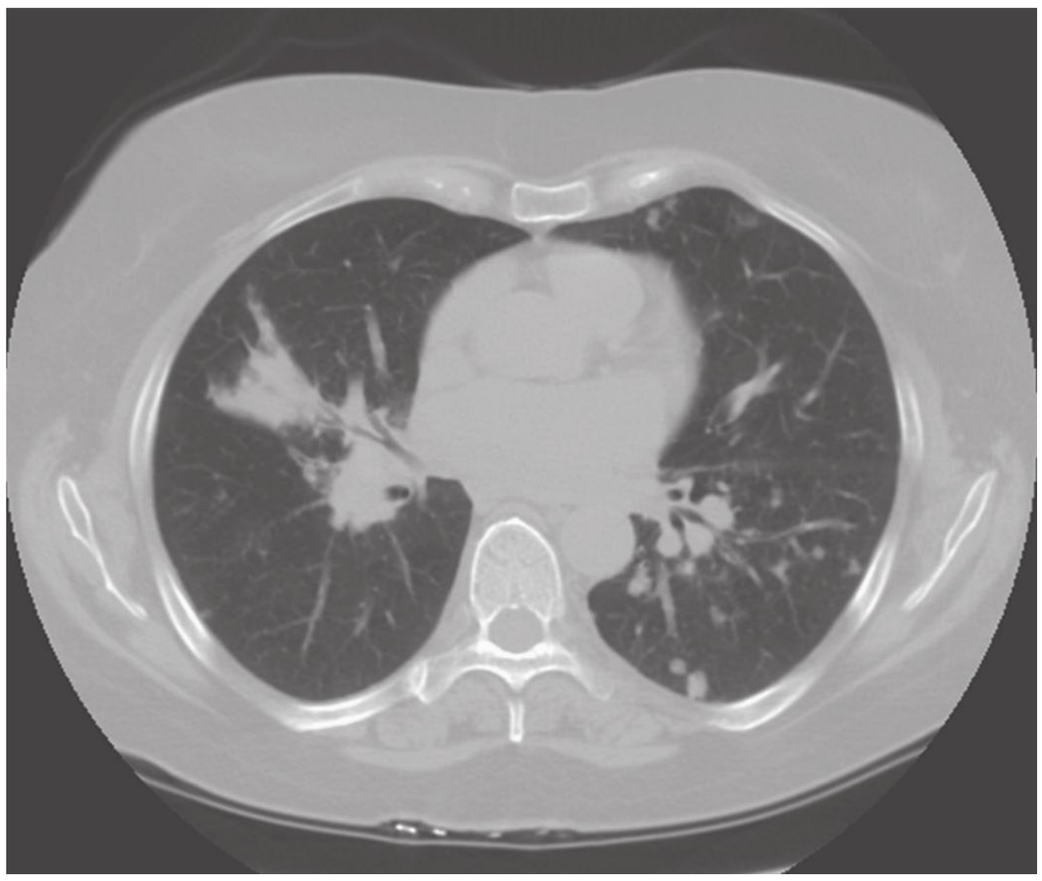


FIGURE 14-3
High-resolution computed tomography scan of chest demonstrating patchy reticular nodularity, including areas of confuence.

the differential diagnosis of upper lobe disease includes hypersensitivity pneumonitis, silicosis, and Langerhans cell histiocytosis. For infectious diseases, tuberculosis and Pneumocystis pneumonia can often present as upper lobe diseases.

Lung volumes, mechanics, and diffusion are all useful in evaluating interstitial lung diseases such as sarcoidosis. The diffusion of carbon monoxide (DL_{CO}) is the most sensitive test for an interstitial lung disease. Reduced lung volumes are a reflection of the restrictive lung disease seen in sarcoidosis. However, a third of the patients presenting with sarcoidosis still have lung volumes within the normal range, despite abnormal chest roentgenograms and dyspnea.

Approximately one-half of sarcoidosis patients present with obstructive disease, reflected by a reduced ratio of forced vital capacity expired in 1 second (FEV_1/FVC). Cough is a very common symptom. Airway involvement causing varying degrees of obstruction underlies the cough in most sarcoidosis patients. Airway hyperreactivity, as determined by methacholine challenge, will be positive in some of these patients. A few patients with cough will respond to traditional bronchodilators as the only form of treatment. In some cases, high-dose inhaled glucocorticoids alone are useful. Airway obstruction can be due to large airway stenosis, which can become fibrotic and unresponsive to anti-inflammatory therapy.

Pulmonary arterial hypertension is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension. In sarcoidosis patients with end-stage fibrosis awaiting lung transplant, 70% will have pulmonary arterial hypertension. This is a much higher incidence than that reported for other fibrotic lung diseases. In less advanced, but still symptomatic, patients, pulmonary arterial hypertension has been noted in up to 50% of the cases. Because sarcoidosis-associated pulmonary arterial hypertension may respond to therapy, evaluation for this should be considered in persistently dyspneic patients.

SKIN

Skin involvement is eventually identified in over a third of patients with sarcoidosis. The classic cutaneous lesions include erythema nodosum, maculopapular lesions, hyper- and hypopigmentation, keloid formation, and subcutaneous nodules. A specific complex of involvement of the bridge of the nose, the area beneath the eyes, and the cheeks is referred to as lupus pernio **(Fig. 14-4)** and is diagnostic for a chronic form of sarcoidosis.

In contrast, erythema nodosum is a transient rash that can be seen in association with hilar adenopathy and uveitis (Löfgren's syndrome). Erythema nodosum is more common in women and in certain self-described demographic groups including whites and Puerto Ricans. In the United States, the other manifestations of skin sarcoidosis, especially lupus pernio, are more common in African Americans than whites.

The maculopapular lesions from sarcoidosis are the most common chronic form of the disease **(Fig. 14-5)**. These are often overlooked by the patient and physician, because they are chronic and not painful. Initially, these



FIGURE 14-4
Chronic inflammatory lesions around nose, eyes, and cheeks, referred to as lupus pernio.



FIGURE 14-5
Maculopapular lesions on the trunk of a sarcoidosis patient.

lesions are usually purplish papules and are often indurated. They can become confluent and infiltrate large areas of the skin. With treatment, the color and induration may fade. Because these lesions are caused by noncaseating granulomas, the diagnosis of sarcoidosis can be readily made by a skin biopsy.

EYE

The frequency of ocular manifestations for sarcoidosis varies depending on race. In Japan, >70% of sarcoidosis patients develop ocular disease, whereas in the United States only 30% have eye disease, with problems more common in African Americans than whites. Although the most common manifestation is an anterior uveitis, over a quarter of patients will have inflammation at the posterior of the eye, including retinitis and pars planitis. Although symptoms such as photophobia, blurred vision, and increased tearing can occur, some asymptomatic patients still have active inflammation. Initially asymptomatic patients with ocular sarcoidosis can eventually develop blindness. Therefore, it is recommended that all patients with sarcoidosis receive a dedicated ophthalmologic examination. Sicca is seen in over one-half of the chronic sarcoidosis patients. Dry eyes appear to be a reflection of prior lacrimal gland disease. Although the patient may no longer have active inflammation, the dry eyes may require natural tears or other lubricants.

LIVER

Using biopsies to detect granulomatous disease, liver involvement can be identified in over one-half of sarcoidosis patients. However, using liver function studies, only 20–30% of patients will have evidence of liver involvement. The most common abnormality of liver function is an elevation of the alkaline phosphatase level, consistent with an obstructive pattern. In addition, elevated transaminase levels can occur. An elevated bilirubin level is a marker for more advanced liver disease. Overall, only 5% of sarcoidosis patients have sufficient symptoms from their liver disease to require specific therapy. Although symptoms can be due to hepatomegaly, more frequently symptoms result from extensive intrahepatic cholestasis leading to portal hypertension. In this case, ascites and esophageal varices can occur. It is rare that a sarcoidosis patient will require a liver transplant, because even the patient with cirrhosis due to sarcoidosis can respond to systemic therapy. On a cautionary note, patients with both sarcoidosis and hepatitis C should avoid therapy with interferon a because of its association with the development or worsening of granulomatous disease.

BONE MARROW AND SPLEEN

One or more bone marrow manifestations can be identified in many sarcoidosis patients. The most common hematologic problem is lymphopenia, which is a reflection of sequestration of the lymphocytes into the areas of inflammation. Anemia occurs in 20% of patients, and leukopenia is less common. Bone marrow examination will reveal granulomas in about a third of patients. Although splenomegaly can be detected in 5–10% of patients, splenic biopsy reveals granulomas in 60% of patients. The CT scan can be relatively specific for sarcoidosis involvement of the spleen **(Fig. 14-6)**. Both

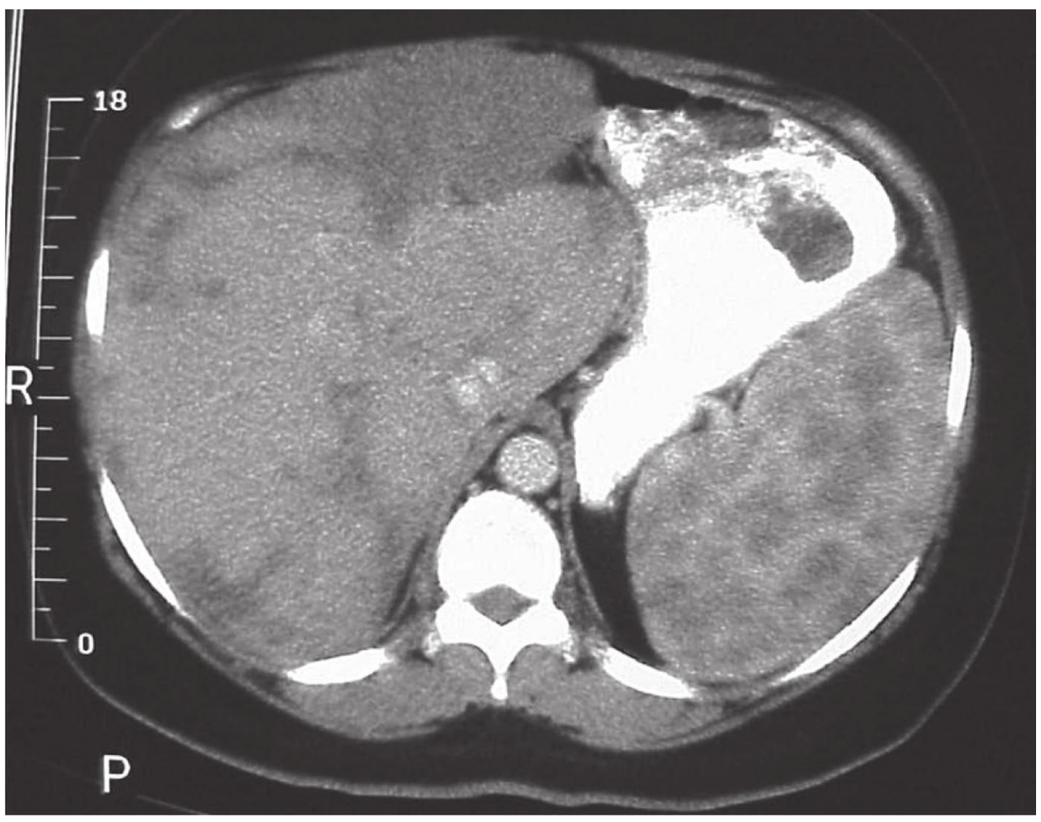


FIGURE 14-6
Computed tomography scan of the abdomen after oral and intravenous contrast. The stomach is compressed by the enlarged spleen. Within the spleen, areas of hypo- and hyperdensity are identified.

bone marrow and spleen involvement are more common in African Americans than whites. Although these manifestations alone are rarely an indication for therapy, on rare occasion, splenectomy may be indicated for massive symptomatic splenomegaly or profound pancytopenia. Nonthoracic lymphadenopathy can occur in up to 20% of patients.

CALCIUM METABOLISM

Hypercalcemia and/or hypercalciuria occurs in about 10% of sarcoidosis patients. It is more common in whites than African Americans and in men. T e mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself. T e 1,25-dihydroxyvitamin D causes increased intestinal absorption of calcium, leading to hypercalcemia with a suppressed parathyroid hormone (PTH) level. Increased exogenous vitamin D from diet or sunlight exposure may exacerbate this problem. Serum calcium should be determined as part of the initial evaluation of all sarcoidosis patients, and a repeat determination may be useful during the summer months with increased sun exposure. In patients with a history of renal calculi, a 24-h urine calcium measurement should be obtained. If a sarcoidosis patient with a history of renal calculi is to be placed on calcium supplements, a follow-up 24-h urine calcium level should be measured.

RENAL DISEASE

Direct kidney involvement occurs in <5% of sarcoidosis patients. It is associated with granulomas in the kidney itself and can lead to nephritis. However, hypercalcemia is the most likely cause of sarcoidosis-associated renal disease. In 1–2% of sarcoidosis patients, acute renal failure may develop as a result of hypercalcemia. Successful treatment of hypercalcemia with glucocorticoids and other therapies often improves but usually does not totally resolve the renal dysfunction.

NERVOUS SYSTEM

Neurologic disease is reported in 5–10% of sarcoidosis patients and appears to be of equal frequency across all ethnic groups. Any part of the central or peripheral nervous system can be affected. T e presence of granulomatous inflammation is often visible on magnetic resonance imaging (MRI) studies. T e MRI with gadolinium enhancement may demonstrate space-occupying lesions, but the MRI can be negative due to small lesions or the effect of systemic therapy in reducing the inflammation. T e cerebral spinal fluid (CSF) findings include lymphocytic meningitis with a mild increase in protein. T e CSF glucose is usually normal but can be low. Certain areas of the nervous system are more commonly affected in neurosarcoidosis. T ese include cranial nerve involvement, basilar meningitis, myelopathy, and anterior hypothalamic disease with associated diabetes insipidus. Seizures and cognitive changes also occur. Of the cranial nerves, seventh nerve paralysis can be transient and mistaken for Bell's palsy (idiopathic seventh nerve paralysis). Because this form of neurosarcoidosis often resolves within weeks and may not recur, it may have occurred prior to a definitive diagnosis of sarcoidosis. Optic neuritis is another cranial nerve manifestation of sarcoidosis. T is manifestation is more chronic and usually requires long-term systemic therapy. It can be associated with both anterior and posterior uveitis. Differentiating between neurosarcoidosis and multiple sclerosis can be dif cult at times. Optic neuritis can occur in both diseases. In some patients with sarcoidosis, multiple enhancing white matter abnormalities may be detected by MRI, suggesting multiple sclerosis. In such cases, the presence of meningeal enhancement or hypothalamic involvement suggests neurosarcoidosis, as does evidence of extraneurologic disease such as pulmonary or skin involvement, which also suggests sarcoidosis. Because the response of neurosarcoidosis to glucocorticoids and cytotoxic therapy is different from that of multiple sclerosis, differentiating between these disease entities is important.

CARDIAC

T e presence of cardiac involvement is influenced by race. Although over a quarter of Japanese sarcoidosis patients develop cardiac disease, only 5% of sarcoidosis patients in the United States and Europe develop symptomatic cardiac disease. However, there is no apparent racial predilection between whites and African Americans. Cardiac disease, which usually presents as either congestive heart failure or cardiac arrhythmias, results from infiltration of the heart muscle by granulomas. Diffuse granulomatous involvement of the heart muscle can lead to profound dysfunction with left ventricular ejection fractions below 10%. Even in this situation, improvement in the ejection fraction can occur with systemic therapy. Arrhythmias can also occur with diffuse infiltration or with more patchy cardiac involvement. If the atrioventricular (AV) node is infiltrated, heart block can occur, which can be detected by routine electrocardiography. Ventricular arrhythmias and sudden death due to ventricular tachycardia are common causes of death. Arrhythmias are best detected using 24-h ambulatory monitoring, and electrophysiology studies may be negative. Other screening tests for cardiac disease include routine electrocardiography and echocardiography. T e confirmation of cardiac

sarcoidosis is usually performed with either MRI or positron emission tomography (PET) scanning. Because ventricular arrhythmias are usually multifocal due to patchy multiple granulomas in the heart, ablation therapy is not useful. Patients with significant ventricular arrhythmias should be considered for an implanted defibrillator, which appears to have reduced the rate of death in cardiac sarcoidosis. Although systemic therapy can be useful in treating the arrhythmias, patients may still have malignant arrhythmias up to 6 months after starting successful treatment, and the risk for recurrent arrhythmias occurs whenever medications are tapered.

MUSCULOSKELETAL SYSTEM

Direct granulomatous involvement of bone and muscle can be documented by radiography (x-ray, MRI, PET scan **[Fig. 14-7]**, or gallium scan) or confirmed by biopsy in about 10% of sarcoidosis patients. However, a larger percentage of sarcoidosis patients complain of myalgias and arthralgias. T ese complaints are similar to those reported by patients with other inflammatory diseases, including chronic infections such as mononucleosis. Fatigue associated with sarcoidosis may be overwhelming for many patients. Recent studies have demonstrated a link between fatigue and small peripheral nerve fiber disease in sarcoidosis.

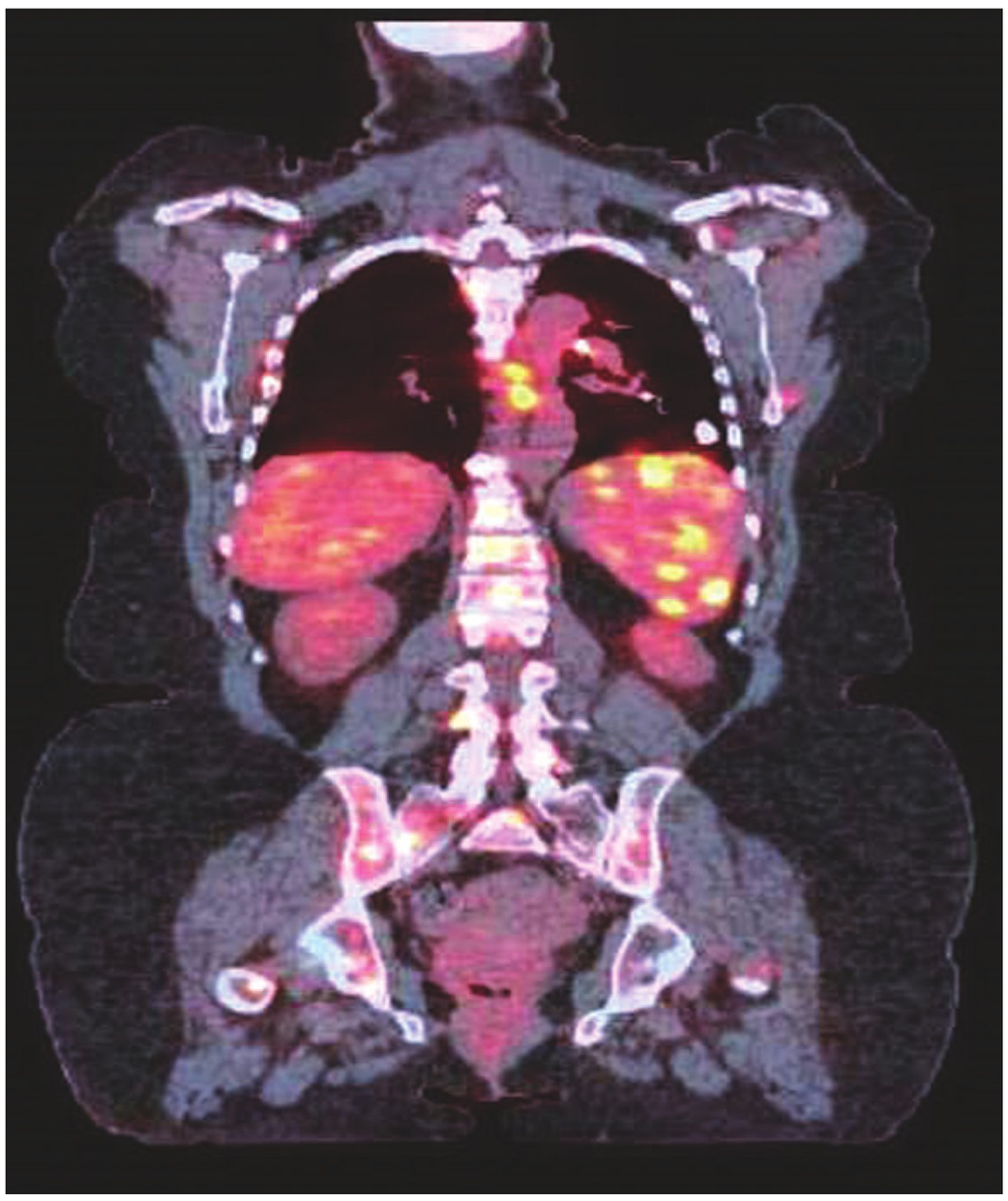


FIGURE 14-7
Positron emission tomography and computed tomography scan merged demonstrating increased activity in spleen, ribs, and spine of patient with sarcoidosis.

OTHER ORGAN INVOLVEMENT

Although sarcoidosis can affect any organ of the body, rarely does it involve the breast, testes, ovary, or stomach. Because of the rarity of involvement, a mass in one of these areas requires a biopsy to rule out other diseases including cancer. For example, in a study of breast problems in female sarcoidosis patients, a breast lesion was more likely to be a granuloma from sarcoidosis than from breast cancer. However, findings on the physical examination or mammogram cannot reliably differentiate between these lesions. More importantly, as women with sarcoidosis age, breast cancer becomes more common. T erefore, it is recommended that routine screening including mammography be performed along with other imaging studies (ultrasound, MRI) or biopsy as clinically indicated.

COMPLICATIONS

Sarcoidosis is usually a self-limited, non-life-threatening disease. However, organ-threatening disease can occur. T ese complications can include blindness, paraplegia, or renal failure. Death from sarcoidosis occurs in about 5% of patients seen in sarcoidosis referral clinics. T e usual causes of death related to sarcoidosis are from lung, cardiac, neurologic, or liver involvement. In respiratory failure, an elevation of the right atrial pressure is a poor prognostic finding. Lung complications can also include infections such as mycetoma, which can subsequently lead to massive bleeding. In addition, the use of immunosuppressive agents can increase the incidence of serious infections.

LABORATORY FINDINGS

T e chest roentgenogram remains the most commonly used tool to assess lung involvement in sarcoidosis. As noted above, the chest roentgenogram classifies involvement into four stages, with stages 1 and 2 having hilar and paratracheal adenopathy. T e CT scan has been used increasingly in evaluating interstitial lung disease. In sarcoidosis, the presence of adenopathy and a nodular infiltrate is not specific for sarcoidosis. Adenopathy up to 2 cm can be seen in other inflammatory lung diseases such as idiopathic pulmonary fibrosis. However, adenopathy >2 cm in the short axis supports the diagnosis of sarcoidosis over other interstitial lung diseases.

T e PET scan has increasingly replaced gallium-67 scanning to identify areas of granulomatous disease in the chest and other parts of the body (Fig. 14-7). Both

tests can be used to identify potential areas for biopsy. Cardiac PET scanning has also proved useful in assessing cardiac sarcoidosis. T e identification of hypermetabolic activity may be due to the granulomas from sarcoidosis and not to disseminated malignancy.

MRI has also proved useful in the assessment of extrapulmonary sarcoidosis. Gadolinium enhancement has been demonstrated in areas of inflammation in the brain, heart, and bone. MRI scans may detect asymptomatic lesions. Like PET scan, MRI changes appear similar to those seen with malignancy and infection. In some cases, biopsy may be necessary to determine the cause of the radiologic abnormality.

Serum levels of angiotensin-converting enzyme (ACE) can be helpful in the diagnosis of sarcoidosis. However, the test has somewhat low sensitivity and specificity. Elevated levels of ACE are reported in 60% of patients with acute disease and only 20% of patients with chronic disease. Although there are several causes for mild elevation of ACE, including diabetes, elevations of >50% of the upper limit of normal are seen in only a few conditions including sarcoidosis, leprosy, Gaucher's disease, hyperthyroidism, and disseminated granulomatous infections such as miliary tuberculosis. Because the ACE level is determined by a biologic assay, the concurrent use of an ACE inhibitor such as lisinopril will lead to a very low ACE level.

DIAGNOSIS

T e diagnosis of sarcoidosis requires both compatible clinical features and pathologic findings. Because the cause of sarcoidosis remains elusive, the diagnosis cannot be made with 100% certainty. Nevertheless, the diagnosis can be made with reasonable certainty based on history and physical features along with laboratory and pathologic findings.

Patients are usually evaluated for possible sarcoidosis based on two scenarios **(Fig. 14-8)**. In the first scenario, a patient may undergo a biopsy revealing a noncaseating granuloma in either a pulmonary or an extrapulmonary organ. If the clinical presentation is consistent with sarcoidosis and there is no alternative cause for the granulomas identified, then the patient is felt to have sarcoidosis.

In the second scenario, signs or symptoms suggesting sarcoidosis such as the presence of bilateral adenopathy may be present in an otherwise asymptomatic patient or a patient with uveitis or a rash consistent with sarcoidosis. At this point, a diagnostic procedure should be performed. For the patient with a compatible skin lesion, a skin biopsy should be considered. Other biopsies to consider could include liver, extrathoracic lymph node, or muscle. In some cases, a biopsy of the affected organ may not be easy to perform (such as a brain or

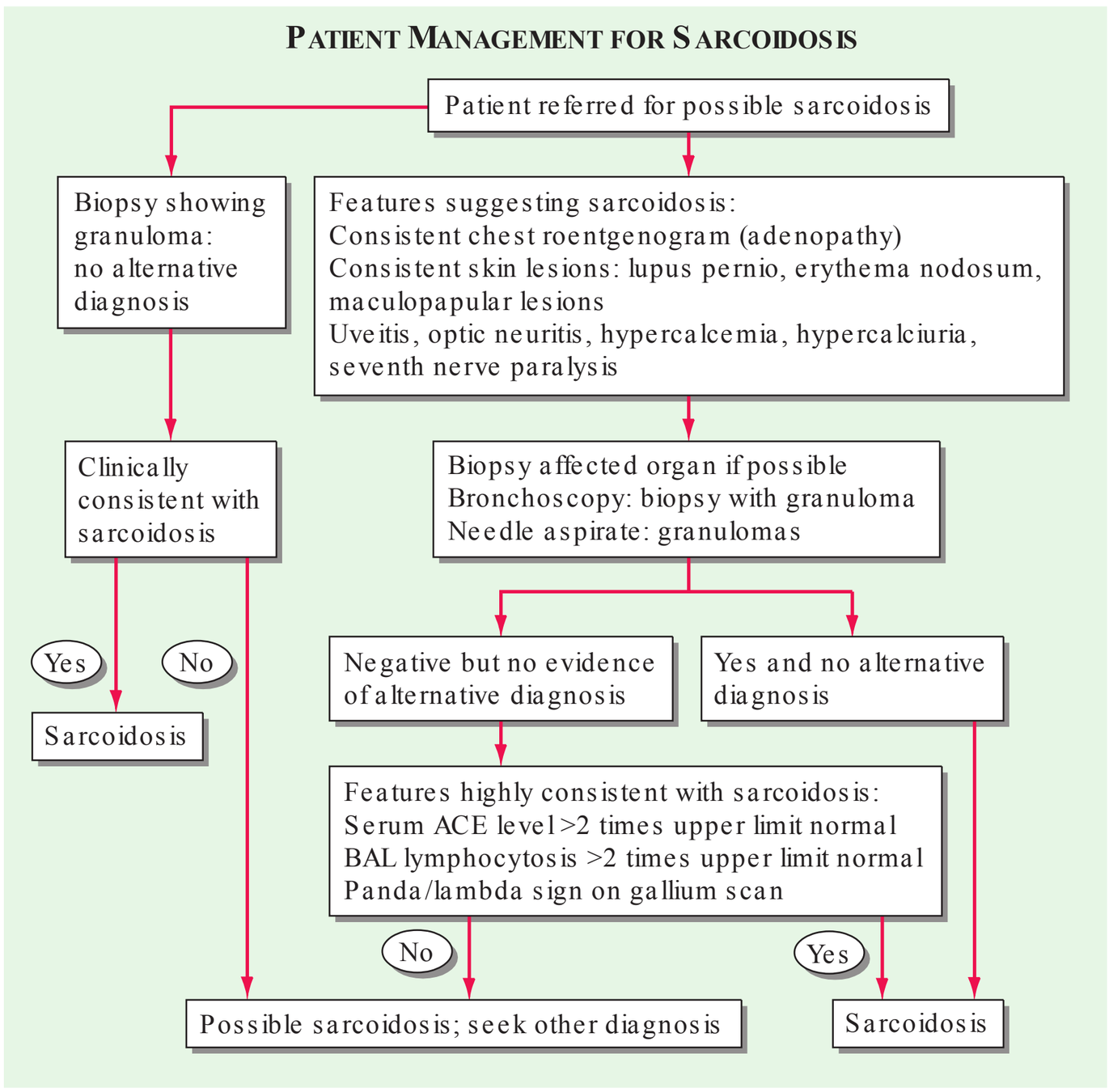


FIGURE 14-8
Proposed approach to management of patient with possible sarcoidosis. Presence of one or more of these features supports the diagnosis of sarcoidosis: uveitis, optic neuritis, hypercalcemia, hypercalciuria, seventh cranial nerve paralysis, diabetes insipidus. ACE, angiotensin-converting enzyme; BAL, bronchoalveolar lavage.

spinal cord lesion). In other cases, such as an endomyocardial biopsy, the likelihood of a positive biopsy is low. Because of the high rate of pulmonary involvement in these cases, the lung may be easier to approach by bronchoscopy. During the bronchoscopy, a transbronchial biopsy, bronchial biopsy, or transbronchial needle aspirate can be performed. T e endobronchial ultrasonography-guided (EBUS) transbronchial needle aspirate can assist in diagnosing sarcoidosis in patients with mediastinal adenopathy (stage 1 or 2 radiographic pulmonary disease), whereas transbronchial biopsy has a higher diagnostic yield for those with only parenchymal lung disease (stage 3). T ese tests are complementary and may be performed together.

If the biopsy reveals granulomas, an alternative diagnosis such as infection or malignancy must be excluded. Bronchoscopic washings can be sent for cultures for fungi and tuberculosis. For the pathologist, the more tissue that is provided, the more comfortable is the diagnosis of sarcoidosis. A needle aspirate may be adequate in an otherwise classic case of sarcoidosis, but may be insuf cient in a patient in whom lymphoma or fungal infection is a likely alternative diagnosis. Because granulomas can be seen on the edge of a lymphoma, the presence of a few granulomas from a needle aspirate may not be suf cient to clarify the diagnosis. Mediastinoscopy provides a larger sample to confirm the presence or absence of lymphoma in the mediastinum. Alternatively, for most patients, evidence of extrathoracic disease (e.g., eye involvement) may further support the diagnosis of sarcoidosis.

For patients with negative pathology, positive supportive tests may increase the likelihood of the diagnosis of sarcoidosis. T ese tests include an elevated ACE level, which can also be elevated in other granulomatous diseases but not in malignancy. A positive PET scan can support the diagnosis if multiple organs are affected. A BAL is often performed during the bronchoscopy. An increase in the percentage of lymphocytes supports the diagnosis of sarcoidosis. T e use of the lymphocyte markers CD4 and CD8 can be used to determine the CD4/CD8 ratio of these increased lymphocytes in the BAL fluid. A ratio of >3.5 is strongly supportive of sarcoidosis but is less sensitive than an increase in lymphocytes alone. Although in general, an increase in BAL lymphocytes is supportive of the diagnosis, other conditions must be considered.

Supportive findings, when combined with commonly associated but nondiagnostic clinical features of the disease, improve the diagnostic probability of sarcoidosis. T ese clinical features include uveitis, renal stones, hypercalcemia, seventh cranial nerve paralysis, or erythema nodosum. T e presence of one or more of these features in a patient suspected of having sarcoidosis increases the probability of sarcoidosis.

T e Kviem-Siltzbach procedure is a specific diagnostic test for sarcoidosis. An intradermal injection of specially prepared tissue derived from the spleen of a known sarcoidosis patient is biopsied 4–6 weeks after injection. If noncaseating granulomas are seen, this is highly specific for the diagnosis of sarcoidosis. Unfortunately, there is no commercially available Kviem-Siltzbach reagent, and some locally prepared batches have lower specificity. T us, this test is of historic interest and is rarely used in current clinical practice.

Because the diagnosis of sarcoidosis can never be certain, over time other features may arise that lead to an alternative diagnosis. Conversely, evidence for new organ involvement may eventually confirm the diagnosis of sarcoidosis.

PROGNOSIS

T e risk of death or loss of organ function remains low in sarcoidosis. Poor outcomes usually occur in patients who present with advanced disease in whom treatment seems to have little impact. In these cases, irreversible fibrotic changes have frequently occurred. Over the past 20 years, the reported mortality from sarcoidosis has increased in the United States and England. Whether this is due to heightened awareness of the chronic nature of this disease or to other factors such as more widespread immunosuppressive therapy usage remains unclear.

For the majority of patients, initial presentation occurs during the granulomatous phase of the disease as depicted in Fig. 14-1. It is clear that many patients resolve their disease within 2–5 years. T ese patients are felt to have acute, self-limiting sarcoidosis. However, there is a form of the disease that does not resolve within the first 2–5 years. T ese chronic patients can be identified at presentation by certain risk factors at presentation such as fibrosis on chest roentgenogram, presence of lupus pernio, bone cysts, cardiac or neurologic disease (except isolated seventh nerve paralysis), and presence of renal calculi due to hypercalciuria. Recent studies also indicate that patients who require glucocorticoids for any manifestation of their disease in the first 6 months of presentation have a >50% chance of having chronic disease. In contrast, <10% of patients who require no systemic therapy in the first 6 months will require chronic therapy.

TREATMENT Sarcoidosis

Indications for therapy should be based on symptoms or presence of organ- or life-threatening disease, including disease involving the eye, heart, or nervous system. T e patient

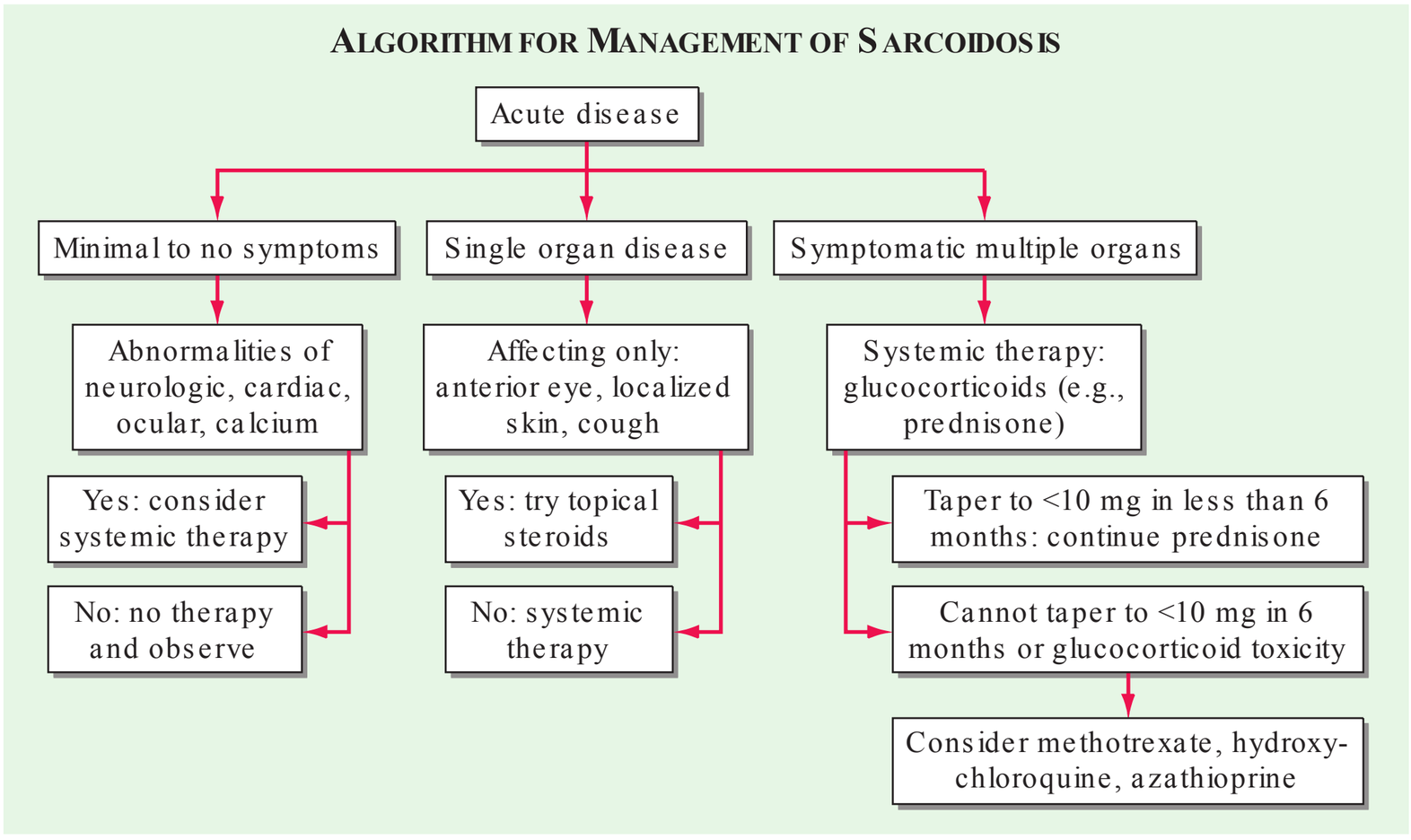


FIGURE 14-9
The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In patients with mild symptoms, no therapy may be needed unless specified manifestations are noted.

with asymptomatic elevated liver function tests or an abnormal chest roentgenogram probably does not benefit from treatment. However, these patients should be monitored for evidence of progressive, symptomatic disease.

One approach to therapy is summarized in **Figs. 14-9** and **14-10.** We have divided the approach into treating acute versus chronic disease. For acute disease, no therapy remains a viable option for patients with no or mild symptoms. For symptoms confined to only one organ, topical therapy is preferable. For multiorgan disease or disease too extensive for topical therapy, an approach to systemic therapy is outlined. Glucocorticoids remain the drugs of choice for this disease. However, the decision to continue to treat with glucocorticoids or to add steroid-sparing agents depends on the tolerability, duration, and dosage of glucocorticoids. **Table 14-2** summarizes the dosage and monitoring of several commonly used drugs. According to the available trials, evidence-based recommendations are made. Most of these recommendations are for pulmonary disease because most of the trials were performed only in pulmonary disease. Treatment recommendations for extrapulmonary disease are usually similar with a few modifications. For example, the dosage of glucocorticoids is usually higher for neurosarcoidosis and lower for cutaneous disease. There was some suggestion that higher doses

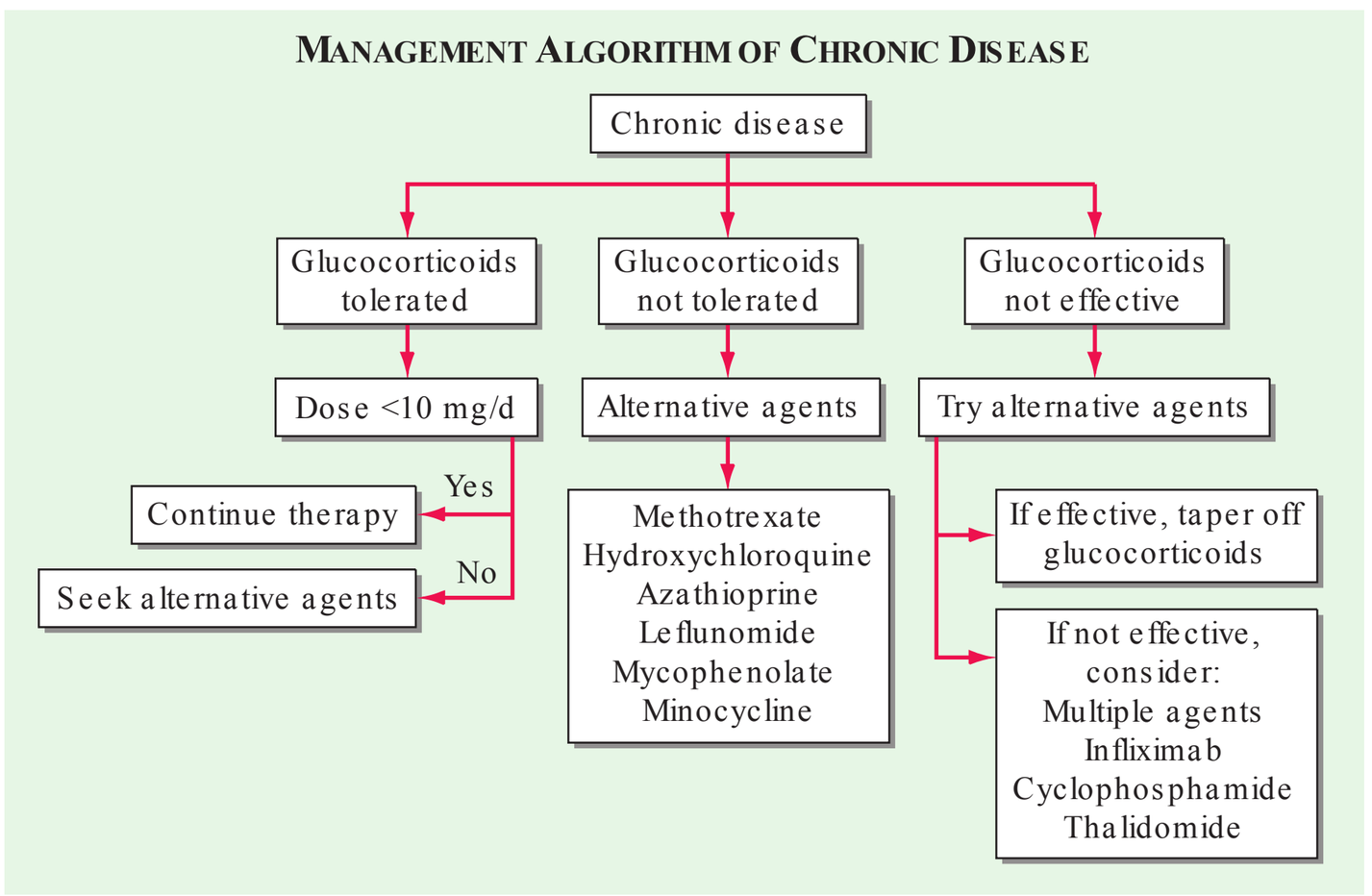


FIGURE 14-10
Approach to chronic disease is based on whether glucocorticoid therapy is tolerated or not.

TABLE 14-2

COMMONLY USED DRUGS TO TREAT SARCOIDOSIS

DRUG	INITIAL DOSE	MAINTENANCE DOSE	MONITORING	TOXICITY	SUPPORT THERAPY[a]	SUPPORT MONITORING[a]
Prednisone	20–40 mg qd	Taper to 5–10 mg	Glucose, blood pressure, bone density	Diabetes, osteoporosis	A: Acute pulmonary D: Extrapulmonary	
Hydroxychloroquine	200–400 mg qd	400 mg qd	Eye exam q6–12 mo	Ocular	B: Some forms of disease	D: Routine eye exam
Methotrexate	10 mg qwk	2.5–15 mg qwk	CBC, renal, hepatic q2mo	Hematologic, nausea, hepatic, pulmonary	B: Steroid sparing C: Some forms chronic disease	D: Routine hematologic, renal, and hepatic monitoring
Azathioprine	50–150 mg qd	50–200 mg qd	CBC, renal q2mo	Hematologic, nausea	C: Some forms chronic disease	D: Routine hematologic monitoring
Infliximab	3–5 mg/kg q2wk for 2 doses	3–10 mg/kg q4–8 wk	Initial PPD	Infections, allergic reaction, carcinogen	A: Chronic pulmonary disease	B: Caution in patients with latent tuberculosis or advanced congestive heart failure

[a]Grade A: supported by at least two double-blind randomized control trials; grade B: supported by prospective cohort studies; grade C: supported primarily by two or more retrospective studies; grade D: only one retrospective study or based on experience in other diseases.
Abbreviations: CBC, complete blood count; PPD, purified protein derivative test for tuberculosis.
Source: Adapted from RP Baughman, O Selroos: Evidence-based approach to treatment of sarcoidosis, in PG Gibson et al (eds): Evidence-Based Respiratory Medicine. Oxford, BMJ Books Blackwell, 2005, pp 491–508.

would be beneficial for cardiac sarcoidosis, but one study found that initial prednisone doses >40 mg/d were associated with a worse outcome because of toxicity.

Systemic therapies for sarcoidosis are usually immunosuppressive including glucocorticoids, cytotoxics, or biologics. Although most patients receive glucocorticoids as their initial systemic therapy, toxicity associated with prolonged therapy often leads to steroid-sparing alternatives. The antimalarial drugs such as hydroxychloroquine are more effective for skin than pulmonary disease. Minocycline may also be useful for cutaneous sarcoidosis. For pulmonary and other extrapulmonary disease, cytotoxic agents are often used. These include methotrexate, azathioprine, leflunomide, mycophenolate, and cyclophosphamide. The most widely studied cytotoxic agent has been methotrexate. This agent works in approximately two-thirds of sarcoidosis patients, regardless of the disease manifestation. In one retrospective study comparing methotrexate to azathioprine, both drugs were equally effective. However, methotrexate was associated with significantly less toxicity. As noted in Table 14-2, specific guidelines for monitoring therapy have been recommended. Cytokine modulators such as thalidomide and pentoxifylline have also been used in a limited number of cases.

The biologic anti-TNF agents have recently been studied in sarcoidosis, with prospective randomized trials completed for both etanercept and infliximab. Etanercept has a limited role as a steroid-sparing agent. Conversely, infliximab significantly improved lung function when administered to glucocorticoid and cytotoxic pretreated patients with chronic disease The difference in response between these two agents is similar to that observed in Crohn's disease, where infliximab is effective and etanercept is not. However, there is a higher risk for reactivation of tuberculosis with infliximab compared to etanercept. The differential response rate could be explained by differences in mechanism of action because etanercept is a TNF receptor antagonist and infliximab is a monoclonal antibody against TNF. In contrast to etanercept, infliximab also binds to TNF on the surface of some cells that release TNF, which leads to cell lysis. This effect has been documented in Crohn's disease. Adalimumab is a humanized monoclonal anti-TNF antibody that also appears effective for sarcoidosis when dosed at higher strengths, as recommended for the treatment of Crohn's disease. The role of the newer therapeutic agents for sarcoidosis is still evolving. However, these targeted therapies confirm that TNF may be an important target, especially in the treatment of chronic disease. However, these agents are not a panacea, because sarcoidosis-like disease has occurred in patients treated with anti-TNF agents for nonsarcoidosis indications.

CHAPTER 15

IgG4-RELATED DISEASE

John H. Stone

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by a tendency to form tumefactive lesions. The clinical manifestations of this disease, however, are protean, and continue to be defined. IgG4-RD has now been described in virtually every organ system. Commonly affected organs are the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, and retroperitoneum. In addition, IgG4-RD involvement of the meninges, aorta, prostate, thyroid, pericardium, skin, and other organs is well described. The disease is believed to affect the brain parenchyma, the joints, the bone marrow, and the bowel mucosa only rarely (if ever).

The clinical features of IgG4-RD are numerous, but the pathologic findings are consistent across all affected organs. These findings include a lymphoplasmacytic infiltrate with a high percentage of IgG4-positive plasma cells; a characteristic pattern of fibrosis termed "storiform"; a tendency to target blood vessels, particularly veins, through an obliterative process ("obliterative phlebitis"); and a mild to moderate tissue eosinophilia.

IgG4-RD encompasses a number of conditions previously regarded as separate, organ-specific entities. A condition once known as "lymphoplasmacytic sclerosing pancreatitis" (among many other terms) became the paradigm of IgG4-RD in 2000, when Japanese investigators recognized that these patients had elevated serum concentrations of IgG4. This form of sclerosing pancreatitis is now termed type 1 (IgG4-related) autoimmune pancreatitis (AIP). By 2003, extrapancreatic disease manifestations had been identified in patients with type 1 AIP, and since then, the manifestations of IgG4-RD in many organs have been catalogued. Mikulicz's disease, once considered to be a subset of Sjögren's syndrome that affected the lacrimal, parotid, and submandibular glands, is now considered part of the IgG4-RD spectrum. Similarly, a subset of patients previously diagnosed as having primary sclerosing cholangitis was known to respond well to glucocorticoids, in contrast to the majority of patients with that diagnosis. This is steroid-responsive subset is now explained by the fact that such patients actually have a separate disease, i.e., IgG4-related sclerosing cholangitis. In this manner, the understanding of IgG4-RD has extended to include nearly every specialty of medicine.

CLINICAL FEATURES

The major organ lesions are summarized in **Table 15-1**. IgG4-RD usually presents subacutely, and most patients do not have severe constitutional symptoms. Fevers and dramatic elevations of C-reactive protein are unusual; however, some patients report substantial weight loss occurring over periods of months. Clinically apparent disease can evolve over months, years, or even decades before the manifestations within a given organ becomes sufficiently severe to bring the patient to medical attention. Some patients have disease that is marked by the appearance and then resolution or temporary improvement in symptoms within a particular organ. Other patients accumulate new organ involvement as their disease persists in previously affected organs. Many patients with IgG4-RD are misdiagnosed as having other conditions, particularly malignancies, or their findings are attributed initially to nonspecific inflammation. The disorder is often identified incidentally through radiologic findings or unexpectedly in pathology specimens.

Multiorgan disease may be evident at diagnosis but can also evolve over months to years. Some patients have disease confined to a single organ for many years. Others have either known or subclinical organ involvement at the same time as the major clinical feature. Patients with type 1 AIP may have their major disease focus in the pancreas; however, thorough evaluations by history, physical examination, blood tests, urinalysis, and cross-sectional imaging may demonstrate lacrimal gland enlargement, sialoadenitis,

TABLE 15-1

ORGAN MANIFESTATIONS OF IGG4-RELATED DISEASE

ORGAN	MAJOR CLINICAL FEATURES
Orbits and periorbital tissues	Painless eyelid or periocular tissue swelling; orbital pseudotumor; dacryoadenitis; dacryocystitis; orbital myositis; and mass lesions extending into the pterygopalatine fossa and infiltrating along the trigeminal nerve
Ears, nose, and sinuses	Allergic phenomena (nasal polyps, asthma, allergic rhinitis, peripheral eosinophilia); nasal obstruction, rhinorrhea, anosmia, chronic sinusitis; occasional bone-destructive lesions
Salivary glands	Submandibular and/or parotid gland enlargement (isolated bilateral submandibular gland involvement more common); minor salivary glands sometimes involved
Meninges	Headache, radiculopathy, cranial nerve palsies, or other symptoms resulting from spinal cord compression; tendency to form mass lesions; magnetic resonance imaging shows marked thickening and enhancement of dura
Hypothalamus and pituitary	Clinical syndromes resulting from involvement of the hypothalamus and pituitary, e.g., anterior pituitary hormone deficiency, central diabetes insipidus, or both; imaging reveals thickened pituitary stalk or mass formation on the stalk, swelling of the pituitary gland, or mass formation within the pituitary
Lymph nodes	Generalized lymphadenopathy or localized disease adjacent to a specific affected organ; the lymph nodes involved are generally 1–2 cm in diameter and nontender
Thyroid gland	Riedel's thyroiditis; fibrosing variant of Hashimoto's thyroiditis
Lungs	Asymptomatic finding on lung imaging; cough, hemoptysis, dyspnea, pleural effusion, or chest discomfort; associated with parenchymal lung involvement, pleural disease, or both; four main clinical syndromes: inflammatory pseudotumor, central airway disease, localized or diffuse interstitial pneumonia, and pleuritis; pleural lesions have severe, nodular thickening of the visceral or parietal pleura with diffuse sclerosing inflammation, sometimes associated with pleural effusion
Aorta	Asymptomatic finding on radiologic studies; surprise finding at elective aortic surgery; aortic dissection; clinicopathologic syndromes described include lymphoplasmacytic aortitis of thoracic or abdominal aorta, aortic dissection, periaortitis and periarteritis, and inflammatory abdominal aneurysm
Retroperitoneum	Backache, lower abdominal pain, lower extremity edema, hydronephrosis from ureteral involvement, asymptomatic finding on radiologic studies
Kidneys	Tubulointerstitial nephritis; membranous glomerulonephritis in a small minority; asymptomatic tumoral lesions, typically multiple and bilateral, are sometimes detected on radiologic studies; renal involvement strongly associated with hypocomplementemia
Pancreas	Type 1 autoimmune pancreatitis, presenting as mild abdominal pain; weight loss; acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass); between 20 and 50% of patients present with acute glucose intolerance; imaging shows diffuse (termed "sausage-shaped pancreas") or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy
Biliary tree	Obstructive jaundice associated with autoimmunity in most cases; weight loss; steatorrhea; abdominal pain; and new-onset diabetes mellitus; mimicker of primary sclerosing cholangitis
Liver	Painless jaundice associated with mild to moderate abdominal discomfort, weight loss, steatorrhea; new-onset diabetes mellitus; mimicker of primary sclerosing cholangitis and cholangiocarcinoma
Other organs involved	Gallbladder, breast (pseudotumor), prostate (prostatism), pericardium (constrictive pericarditis), mesentery (sclerosing mesenteritis), mediastinum (fibrosing mediastinitis), skin (erythematous or flesh-colored papules), peripheral nerve (perineural inflammation)

lymphadenopathy, a variety of pulmonary findings, tubulointerstitial nephritis, hepatobiliary disease, aortitis, retroperitoneal fibrosis, or other organ involvement. Spontaneous improvement, sometimes leading to clinical resolution of certain organ system manifestations, is reported in a small percentage of patients.

Two common characteristics of IgG4-RD are allergic disease and the tendency to form tumefactive lesions that mimic malignancies **(Fig. 15-1)**. Many IgG4-RD patients have allergic features such as atopy, eczema, asthma, nasal polyps, sinusitis, and modest peripheral eosinophilia. IgG4-RD also appears to account for a significant proportion of tumorous swellings—pseudotumors—in many organ systems. Some patients undergo major surgeries (e.g., Whipple procedures or thyroidectomy) for the purpose of resecting malignancies before the



A



B

FIGURE 15-1

A major clinical feature of IgG4-related disease is its tendency to form tumefactive lesions. Shown here are mass lesions of the lacrimal glands (A) and the submandibular glands (B).

correct diagnosis is identified. Frequent sites of pseudotumors are the major salivary glands, lacrimal glands, lungs, and kidneys; however, nearly all organs have been affected with this manifestation.

IgG4-RD often causes major morbidity and can lead to organ failure; however, its general pattern is to cause damage in a subacute manner. Destructive bone lesions in the sinuses, head, and middle ear spaces that mimic granulomatous polyangiitis (formerly Wegener's granulomatosis) also occur in IgG4-RD; less aggressive lesions are the rule in most organs. In regions such as the retroperitoneum, substantial fibrosis often occurs before the diagnosis is established, leading to ureteral entrapment, hydronephrosis, postobstructive uropathy, renal atrophy, and chronic pain, possibly resulting from the encasement of peripheral nerves by the inflammatory process. Undiagnosed or undertreated IgG4-related cholangitis can lead to hepatic failure within months. Similarly, IgG4-related aortitis, believed to be associated with between 10 and 50% of cases of inflammatory aortitis, can cause aneurysms and dissections. Substantial renal dysfunction and even renal failure can ensue from IgG4-related tubulointerstitial nephritis, and renal atrophy is a frequent sequel to this disease complication.

SEROLOGIC FINDINGS

The majority of patients with IgG4-RD have elevated serum IgG4 concentrations; however, the range of elevation varies widely. Serum concentrations of IgG4 as high as 30 or 40 times the upper limit of normal sometimes occur, usually in patients with disease that affects multiple organ systems simultaneously. Approximately 30% of patients have normal serum IgG4 concentrations despite classic histopathologic and immunohistochemical findings. Such patients tend to have disease that affects fewer organs. Patients with IgG4-related retroperitoneal fibrosis have a high likelihood of normal serum IgG4 concentrations, perhaps because the process has advanced to a fibrotic stage by the time the diagnosis is considered.

The correlation between serum IgG4 concentrations and disease activity and the need for treatment is imperfect. Serum IgG4 concentrations typically decline swiftly with the institution of therapy but often do not normalize completely. Patients can achieve clinical remissions yet have persistently elevated serum IgG4 concentrations. Rapidly rising serum IgG4 concentrations may identify patients at greatest risk for clinical flares and monitoring of serial IgG4 concentrations identifies early relapse in some patients; however, the temporal relationship between modest IgG4 elevations and the need for clinical treatment is poor. Clinical relapses occur in some patients despite persistently normal IgG4 concentrations.

IgG4 concentrations in serum are usually measured by nephelometry assays. These assays can lead to reports of spuriously low IgG4 values because of the prozone effect. This effect can be corrected by dilution of the serum sample in the laboratory. The prozone effect should be considered when the results of serologic testing for IgG4 concentrations appear to be at odds with the patient's clinical features.

EPIDEMIOLOGY

The typical patient with IgG4-RD is a middle-aged to elderly man. This epidemiology stands in stark contrast to that of many classic autoimmune conditions, which tend to affect young women. Studies of AIP patients in Japan indicate that the male-to-female ratio in that disease subset is on the order of 3:1. Even more striking,

male predominance has been reported in IgG4-related tubulointerstitial nephritis and IgG4-related retroperitoneal fibrosis. Among IgG4-RD manifestations that involve organs of the head and neck, the sex ratio may be closer to 1:1.

PATHOLOGY

The key histopathology characteristics of IgG4-RD are a dense lymphoplasmacytic infiltrate **(Fig. 15-2)** that is organized in a storiform pattern (resembling a basket-weave), obliterative phlebitis, and a mild to moderate eosinophilic infiltrate. Lymphoid follicles and germinal centers are frequently observed. The infiltrate tends to aggregate around ductal structures when it affects glands such as the lacrimal, submandibular, and parotid glands or the pancreas. The inflammatory lesion often aggregates into tumefactive masses that destroy the involved tissue.

Obliterative arteritis is observed in some organs, particularly the lung; however, venous involvement is more common (and is indeed a hallmark of IgG4-RD). Several histopathology features are uncommon in IgG4-RD and, when detected, mitigate against the diagnosis of IgG4-RD. These include intense neutrophilic infiltration, leukocytoclasis, granulomatous inflammation, multinucleated giant cells, and fibrinoid necrosis.

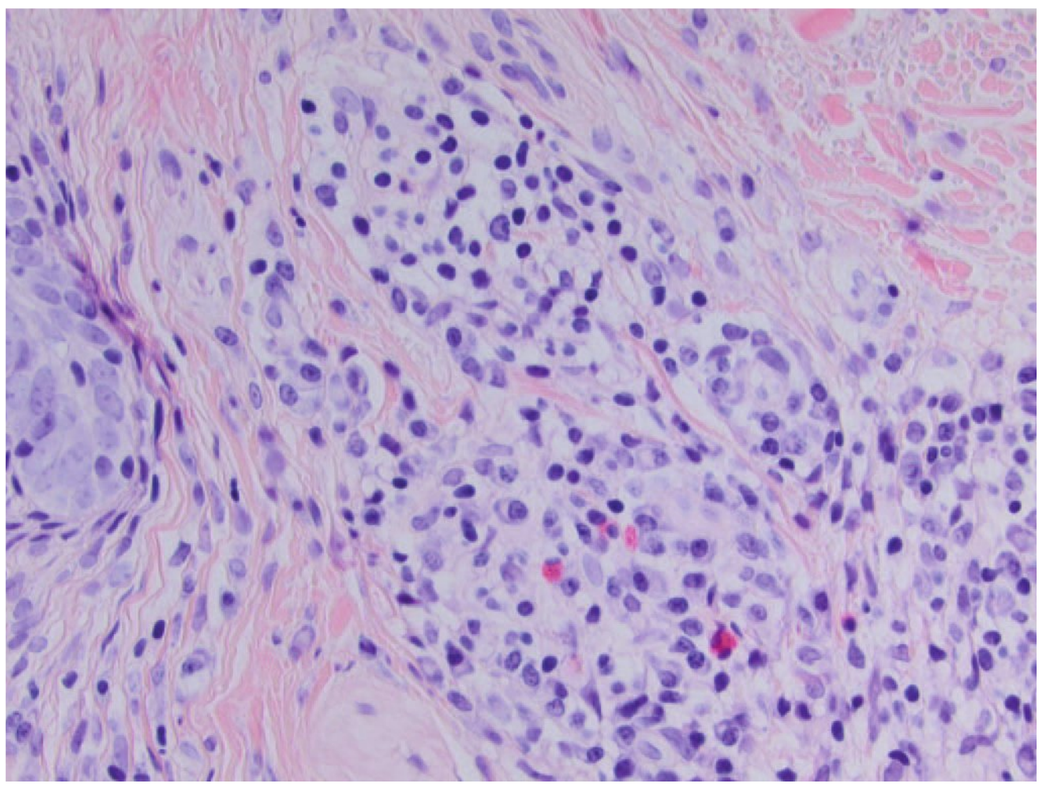


FIGURE 15-2
Hallmark histopathology characteristics of IgG4-related disease (IgG4-RD) are a dense lymphoplasmacytic infiltrate and a mild to moderate eosinophilic infiltrate. The cellular inflammation is often encased in a distinctive type of fibrosis termed "storiform," which often has a basket weave pattern. Abundant fibroblasts and strands of fibrosis accompany the lymphoplasmacytic infiltrate and eosinophils in this figure. This biopsy was taken from a nodular lesion on the cheek; however, the findings are identical to the pathology found in the pancreas, kidneys, lungs, salivary glands, and other organs affected by IgG4-RD.

The inflammatory infiltrate is composed of an admixture of B and T lymphocytes. B cells are typically organized in germinal centers. Plasma cells staining for CD19, CD138, and IgG4 appear to radiate out from the germinal centers. In contrast, the T cells, usually CD4+, are distributed more diffusely throughout the lesion and generally represent the most abundant cell type. Fibroblasts, histiocytes, and eosinophils can all be observed in moderate numbers. Some biopsy samples are particularly enriched with eosinophils. In other samples, particularly from long-standing cases, fibrosis predominates.

The histologic appearance of IgG4-RD, although highly characteristic, requires immunohistochemical confirmation of the diagnosis with IgG4 immunostaining. IgG4-positive plasma cells predominate within the lesion, but plasma cells containing immunoglobulins from each subclass can be found. The number of IgG4-positive plasma cells can be quantified by either counting the number of cells per high-power field (HPF) or by calculating the ratio of IgG4- to IgG-bearing plasma cells. Tissue fibrosis predominates in the latter phases of organ involvement, and in this relatively acellular phase of inflammation, both the IgG4:total IgG ratio and the pattern of tissue fibrosis are more important than the number of IgG4-positive cells per HPF in establishing the diagnosis. In situ hybridization techniques are also now used to circumvent problems posed by increased background staining in conventional immunostaining techniques.

PATHOPHYSIOLOGY

The IgG4 molecule is believed to play an indirect role in the pathophysiology of disease in most organs. However, the molecule has properties that are unique among the immunoglobulin subclasses and that may contribute to tissue injury in some circumstances. As an example, IgG4 molecules have the ability to undergo Fab exchange, a phenomenon in which the two halves of the molecule dissociate from each other and reassociate with dissimilar hemi-molecules from other IgG4 molecules. This property is unique among the immunoglobulin subclasses. Partly as a result of Fab exchange, however, IgG4 antibodies bind antigen loosely. The molecules have low affinities for Fc receptors and C1q and are regarded generally as noninflammatory immunoglobulins. The low affinities for Fc receptors and C1q impair the ability of IgG4 antibodies to induce phagocyte activation, antibody-dependent cellular cytotoxicity, and complement-mediated damage. It is possible that the increased concentrations of IgG4 in serum and IgG4-bearing plasma cells in tissue are merely the result of other effector pathways, such as T_H2/Treg cytokines, that are more central to the inflammation and tissue damage.

TREATMENT

Not every disease manifestation of IgG4-RD requires immediate treatment because the disease takes an indolent form in many patients. IgG4-related lymphadenopathy, for example, can be asymptomatic for years, without evolution to other disease manifestations. T us, watchful waiting is prudent in some cases. Vital organ involvement must be treated aggressively, however, because IgG4-RD can lead to serious organ dysfunction and failure. Aggressive disease can lead quickly to end-stage liver disease, permanent impairment of pancreatic function, renal atrophy, aortic dissection or aneurysms, and destructive lesions in the sinuses and nasopharynx.

Glucocorticoids are the first line of therapy. Treatment regimens, extrapolated from experience with the management of type 1 AIP, generally begin with 40 mg/d of prednisone, with tapering to discontinuation or maintenance doses of 5 mg/d within 2 or 3 months. T e clinical response to glucocorticoids is usually swif and striking; however, longitudinal data indicate that disease flares occur in more than 90% of patients within 3 years. Conventional steroid-sparing agents such as azathioprine and mycophenolate mofetil have been used in some patients; however, evidence for their efficacy is lacking.

For patients with relapsing or glucocorticoid-resistant disease, B cell depletion with rituximab is an excellent second-line therapy. Rituximab treatment (two doses of 1 g IV, separated by approximately 15 days) leads to a targeted, precipitous decline in serum IgG4 concentrations, suggesting that rituximab achieves its effects in part by preventing the repletion of short-lived plasma cells that produce IgG4. More important than its effects on IgG4 concentrations, however, may be the effect of B cell depletion on T cell function. Specific effects of rituximab on CD4+ effector T cells have been documented in IgG4-RD.

Rituximab may be an appropriate first-line therapy for some patients, particularly those at high risk for glucocorticoid toxicity and patients with immediately organ-threatening disease. T e optimal approaches to remission maintenance, by either re-treatment with rituximab or continuous low-dose glucocorticoid therapy, require further study.

CHAPTER 16

FAMILIAL MEDITERRANEAN FEVER AND OTHER HEREDITARY AUTOINFLAMMATORY DISEASES

Daniel L. Kastner

Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases **(Table 16-1)** that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation and, in some individuals, the eventual development of systemic AA amyloidosis. Because of the relative infrequency of high-titer autoantibodies or antigen-specific T cells, the term autoinflammatory has been proposed to describe these disorders, rather than autoimmune. The innate immune system, with its myeloid effector cells and germline receptors for pathogen-associated molecular patterns and endogenous danger signals, plays a predominant role in the pathogenesis of the autoinflammatory diseases. Although the hereditary recurrent fevers comprise a major category of the autoinflammatory diseases, other inherited disorders of inflammation in which recurrent fever plays a less prominent role are now also considered to be autoinflammatory.

BACKGROUND AND PATHOPHYSIOLOGY

FMF was first recognized among Armenians, Arabs, Turks, and non-Ashkenazi (primarily North African and Iraqi) Jews. With the advent of genetic testing, FMF has been documented with increasing frequency among Ashkenazi Jews, Italians, and other Mediterranean populations, and occasional cases have been confirmed even in the absence of known Mediterranean ancestry. FMF is generally regarded as recessively inherited, but there is an increasing awareness of clear-cut clinical cases with only a single demonstrable genetic mutation, and, for certain relatively rare FMF mutations, there is strong evidence for dominant inheritance. Particularly in countries where families are small, a positive family history can only be elicited in ~50% of cases. DNA testing demonstrates carrier frequencies as high as 1:3 among affected populations, suggesting a heterozygote advantage.

The FMF gene encodes a 781-amino acid, ~95 kDa protein denoted pyrin (or marenostrin) that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. The N-terminal 92 amino acids of pyrin define a motif, the PYRIN domain, that is similar in structure to death domains, death effector domains, and caspase recruitment domains. PYRIN domains mediate homotypic protein-protein interactions and have been found in several other proteins, including cryopyrin (NLRP3), which is mutated in three other recurrent fever syndromes. Through a number of mechanisms, including the interaction of the PYRIN domain with an intermediary adaptor protein, pyrin regulates caspase-1 (interleukin [IL] 1β-converting enzyme), and thereby IL-1β secretion. Mice bearing FMF-associated pyrin mutations exhibit inflammation and excessive IL-1 production.

ACUTE ATTACKS

Febrile episodes in FMF may begin even in early infancy; 90% of patients have had their first attack by age 20. Typical FMF episodes generally last 24–72 h, with arthritic attacks tending to last somewhat longer. In some patients, the episodes occur with great regularity, but more often, the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission.

TABLE 16-1

THE HEREDITARY RECURRENT FEVER SYNDROMES

	FMF	TRAPS	HIDS	MWS	FCAS	NOMID
Ethnicity	Jewish, Arab, Turkish, Armenian, Italian	Any ethnic group	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	Recessive[a]	Dominant	Recessive	Dominant	Dominant	Most commonly de novo mutations; somatic mosaicism in a significant minority
Gene/chromosome	MEFV/16p13.3	TNFRSF1A/12p13	MVK/12q24	NLRP3/1q44	NLRP3/1q44	NLRP3/1q44
Protein	Pyrin	p55 TNF receptor	Mevalonate kinase	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)
Attack length	1–3 days	Often >7 days	3–7 days	1–2 days	Minutes–3 days	Continuous, with flares
Serosa	Pleurisy, peritonitis; asymptomatic pericardial effusions	Pleurisy, peritonitis, pericarditis	Abdominal pain, but seldom peritonitis; pleurisy, pericarditis uncommon	Abdominal pain; pleurisy, pericarditis rare	Rare	Rare
Skin	Erysipeloid erythema	Centrifugally migrating erythema	Diffuse maculopapular rash; oral ulcers	Diffuse urticaria-like rash	Cold-induced urticaria-like rash	Diffuse urticaria-like rash
Joints	Acute monoarthritis; chronic hip arthritis (rare)	Acute monoarthritis, arthralgia	Arthralgia, oligoarthritis	Arthralgia, large joint oligoarthritis	Polyarthralgia	Epiphyseal, patellar overgrowth, clubbing
Muscle	Exercise-induced myalgia common; protracted febrile myalgia rare	Migratory myalgia	Uncommon	Myalgia common	Sometimes myalgia	Sometimes myalgia
Eyes, ears	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Uncommon	Conjunctivitis, episcleritis, optic disc edema; sensorineural hearing loss	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness, sensorineural hearing loss
CNS	Aseptic meningitis rare	Headache	Headache	Headache	Headache	Aseptic meningitis, seizures
Amyloidosis	Most common in M694V homozygotes	~15% of cases, most often cysteine mutations, T50M	Uncommon	~25% of cases	Uncommon	Late complication
Treatment	Oral colchicine prophylaxis, IL-1 inhibitors for refractory cases	Glucocorticoids, etanercept, IL-1 inhibitors	NSAIDs for fever; IL-1 and TNF inhibitors	Anakinra, rilonacept, canakinumab	Anakinra, rilonacept, canakinumab	Anakinra

[a] A substantial percentage of patients with clinical FMF have only a single demonstrable MEFV mutation on DNA sequencing.

Abbreviations: FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatories; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children.

Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distention with mild tenderness on direct palpation to severe generalized pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. Computed tomography (CT) scanning may demonstrate a small amount of fluid in the abdominal cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare.

Pleural attacks are usually manifested by unilateral, sharp, stabbing chest pain. Radiographs may show atelectasis and sometimes an effusion. If performed, thoracentesis demonstrates an exudative fluid rich in neutrophils. After repeated attacks, pleural thickening may develop.

FMF arthritis is most frequent among individuals homozygous for the M694V mutation, which is especially common in the non-Ashkenazi Jewish population. Acute arthritis in FMF is usually monoarticular, affecting the knee, ankle, or hip, although other patterns can be seen, particularly in children. Large sterile effusions rich in neutrophils are frequent, without commensurate erythema or warmth. Even after repeated arthritic attacks, radiographic changes are rare. Before the advent of colchicine prophylaxis, chronic arthritis of the knee or hip was seen in ~5% of FMF patients with arthritis. Chronic sacroiliitis can occur in FMF irrespective of the HLA-B27 antigen, even in the face of colchicine therapy. In the United States, FMF patients are much more likely to have arthralgia than arthritis.

T e most characteristic cutaneous manifestation of FMF is erysipelas-like erythema, a raised erythematous rash that most commonly occurs on the dorsum of the foot, ankle, or lower leg alone or in combination with abdominal pain, pleurisy, or arthritis. Biopsy demonstrates perivascular infiltrates of granulocytes and monocytes. T is rash is seen most often in M694V homozygotes and is relatively rare in the United States.

Exercise-induced (nonfebrile) myalgia is common in FMF, and a small percentage of patients develop a protracted febrile myalgia that can last several weeks. Symptomatic pericardial disease is rare, although some patients have small pericardial effusions as an incidental echocardiographic finding. Unilateral acute scrotal inflammation may occur in prepubertal boys. Aseptic meningitis has been reported in FMF, but the causal connection is controversial. Vasculitis, including IgA vasculitis (Henoch-Schönlein) purpura and polyarteritis nodosa **(Chap. 11)**, may be seen at increased frequency in FMF. T e M694V FMF mutation has recently been shown to be a risk factor for Behçet's disease.

Laboratory features of FMF attacks are consistent with acute inflammation and include an elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis (in children), and elevations in C-reactive protein, fibrinogen, haptoglobin, and serum immunoglobulins. Transient albuminuria and hematuria may also be seen.

AMYLOIDOSIS

Before the advent of colchicine prophylaxis, systemic amyloidosis was a common complication of FMF. It is caused by deposition of a fragment of serum amyloid A, an acute-phase reactant, in the kidneys, adrenals, intestine, spleen, lung, and testes. Amyloidosis should be suspected in patients who have proteinuria between attacks; renal or rectal biopsy is used most often to establish the diagnosis. Risk factors include the M694V homozygous genotype, positive family history (independent of FMF mutational status), the SAA 1 genotype, male gender, noncompliance with colchicine therapy, and having grown up in the Middle East.

DIAGNOSIS

For typical cases, physicians experienced with FMF can often make the diagnosis on clinical grounds alone. Clinical criteria sets for FMF have been shown to have high sensitivity and specificity in parts of the world where the pretest probability of FMF is high. Genetic testing can provide a useful adjunct in ambiguous cases or for physicians not experienced in FMF. Most of the more severe disease-associated FMF mutations are in exon 10 of the gene, with a smaller group of milder variants in exon 2. An updated list of mutations for FMF and other hereditary recurrent fevers can be found online at http://*fmf*.igh.cnrs.*fr*/in*f*evers/.

Genetic testing has permitted a broadening of the clinical spectrum and geographic distribution of FMF and may be of prognostic value. Most studies indicate that M694V homozygotes have an earlier age of onset and a higher frequency of arthritis, rash, and amyloidosis. In contrast, the E148Q variant is quite common in certain populations and is more likely to affect overall levels of inflammation than to cause clinical FMF. E148Q is sometimes found in cis with exon 10 mutations, which may complicate the interpretation of genetic test results. Only ~70% of patients with clinically typical FMF have two identifiable mutations in trans. T e inability to identify a second mutation even after intensive molecular analysis suggests that one FMF mutation may be suf cient to cause disease under

some circumstances. In these cases clinical judgment is very important, and sometimes a therapeutic trial of colchicine may help to confirm the diagnosis. Genetic testing of unaffected individuals is usually inadvisable, because of the possibility of nonpenetrance and the potential impact of a positive test on future insurability.

If a patient is seen during his or her first attack, the differential diagnosis may be broad, although delimited by the specific organ involvement. After several attacks the differential diagnosis may include the other hereditary recurrent fever syndromes (Table 16-1); the syndrome of periodic fever with aphthous ulcers, pharyngitis, and cervical adenopathy (PFAPA); systemic-onset juvenile rheumatoid arthritis or adult Still's disease; porphyria; hereditary angioedema; inflammatory bowel disease; and, in women, gynecologic disorders.

TREATMENT Familial Mediterranean Fever

The treatment of choice for FMF is daily oral colchicine, which decreases the frequency and intensity of attacks and prevents the development of amyloidosis in compliant patients. Intermittent dosing at the onset of attacks is not as effective as daily prophylaxis and is of unproven value in preventing amyloidosis. The usual adult dose of colchicine is 1.2–1.8 mg/d, which causes substantial reduction in symptoms in two-thirds of patients and some improvement in >90%. Children may require lower doses, although not proportionately to body weight.

Common side effects of colchicine include bloating, abdominal cramps, lactose intolerance, and diarrhea. They can be minimized by starting at a low dose and gradually advancing as tolerated, splitting the dose, use of simethicone for flatulence, and avoidance of dairy products. If taken by either parent at the time of conception, colchicine may cause a small increase in the risk of trisomy 21 (Down's syndrome). In elderly patients with renal insufficiency, colchicine can cause a myoneuropathy characterized by proximal muscle weakness and elevation of the creatine kinase. Cyclosporine inhibits hepatic excretion of colchicine by its effects on the MDR-1 transport system, sometimes leading to colchicine toxicity in patients who have undergone renal transplantation for amyloidosis. Intravenous colchicine should generally not be administered to patients already taking oral colchicine, because severe, sometimes fatal, toxicity can occur in this setting.

For FMF patients who do not respond to colchicine or cannot tolerate therapeutic doses, injectable IL-1 inhibitors appear to be effective in preventing the acute attacks. In a small randomized placebo-controlled trial, weekly subcutaneous rilonacept, a recombinant IL-1 receptor fusion protein, significantly reduced the frequency of attacks. There is also substantial anecdotal experience with daily subcutaneous anakinra, a recombinant IL-1 receptor antagonist, in preventing the acute attacks of FMF, and in some cases reducing established amyloid deposits. Canakinumab, a monoclonal antibody to IL-1β, and tumor necrosis factor (TNF) inhibitors may also have a role in the treatment of colchicine-unresponsive or intolerant patients. Bone marrow transplantation has been suggested for refractory FMF, but the risk-benefit ratio is currently regarded as unacceptable.

OTHER HEREDITARY RECURRENT FEVERS

Within 5 years of the discovery of the FMF gene, three additional genes causing five other hereditary recurrent fever syndromes were identified, catalyzing a paradigm shift in diagnosis and treatment of these disorders.

TNF RECEPTOR-ASSOCIATED PERIODIC SYNDROME (TRAPS)

TRAPS is caused by dominantly inherited mutations in the extracellular domains of the 55-kDa TNF receptor (TNFR1, p55). Although originally described in a large Irish family (and hence the name *f*amilial Hibernian *f*ever), TRAPS has a broad ethnic distribution. TRAPS episodes often begin in childhood. The duration of attacks ranges from 1–2 days to as long as several weeks, and in severe cases symptoms may be nearly continuous. In addition to peritoneal, pleural, and synovial attacks similar to FMF, TRAPS patients frequently have ocular inflammation (most often conjunctivitis and/or periorbital edema), and a distinctive migratory myalgia with overlying painful erythema may be present. TRAPS patients generally respond better to glucocorticoids than to prophylactic colchicine. Untreated, about 15% develop amyloidosis. The diagnosis of TRAPS is based on the demonstration of TNFRSF1A mutations in the presence of characteristic symptoms. Two particular variants, R92Q and P46L, are common in certain populations and may act more as functional polymorphisms than as disease-causing mutations. In contrast, pathogenic TNFRSF1A mutations, including a number of substitutions at highly conserved cysteine residues, are associated with intracellular TNFR1 misfolding, aggregation, and retention, with consequent ligand-independent kinase activation, mitochondrial reactive oxygen species production, and proinflammatory cytokine release. Etanercept, a TNF inhibitor, ameliorates TRAPS attacks, but the long-term experience with this agent has been less favorable. Perhaps because of the ligand-independent signaling abnormalities in TRAPS, IL-1 inhibition has been beneficial in a large percentage of the patients in whom it has been used. Monoclonal anti-TNF antibodies

should be avoided, because they may exacerbate TRAPS attacks.

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (HIDS)

HIDS is a recessively inherited recurrent fever syndrome found primarily in individuals of northern European ancestry. It is caused by mutations in mevalonate kinase (MVK), encoding an enzyme involved in the synthesis of cholesterol and nonsterol isoprenoids. Attacks usually begin in infancy and last 3–5 days. Clinically distinctive features include painful cervical adenopathy, a diffuse maculopapular rash sometimes affecting the palms and soles, and aphthous ulcers; pleurisy is rare, as is amyloidosis. Although originally defined by the persistent elevation of serum IgD, disease activity is not related to IgD levels, and some patients with FMF or TRAPS may have modestly increased serum IgD. Moreover, occasional patients with MVK mutations and recurrent fever have normal IgD levels. For these reasons, some have proposed renaming this disorder mevalonate kinase deficiency (MKD). All patients with mutations have markedly elevated urinary mevalonate levels during their febrile attacks, although the inflammatory manifestations are likely to be due to a deficiency of isoprenoids rather than an excess of mevalonate. There is currently no established treatment for HIDS/MKD, although intermittent or continuous IL-1 inhibition and TNF inhibitors have been effective in small series.

THE CRYOPYRINOPATHIES, OR CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

Three hereditary febrile syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), are all caused by mutations in NLRP3 (formerly known as CIAS1), the gene encoding cryopyrin (or NLRP3), and represent a clinical spectrum of disease. FCAS patients develop chills, fever, headache, arthralgia, conjunctivitis, and an urticaria-like rash in response to generalized cold exposure. In MWS, an urticarial rash is noted, but it is not usually induced by cold; MWS patients also develop fevers, abdominal pain, limb pain, arthritis, conjunctivitis, and, over time, sensorineural hearing loss. NOMID is the most severe of the three disorders, with chronic aseptic meningitis, a characteristic arthropathy, and rash. Like the FMF protein, pyrin, cryopyrin has an N-terminal PYRIN domain. Cryopyrin regulates IL-1β production through the formation of a macromolecular complex termed the in*fl*ammasome. Peripheral blood leukocytes from patients with FCAS, MWS, and NOMID release increased amounts of IL-1β upon in vitro stimulation, relative to healthy controls. Macrophages from cryopyrin-deficient mice exhibit decreased IL-1β production in response to certain gram-positive bacteria, bacterial RNA, and monosodium urate crystals. Patients with all three cryopyrinopathies show a dramatic response to injections of IL-1 inhibitors. Approximately one-third of patients with clinical manifestations of NOMID do not have germline mutations in NLRP3, but have been found to be mosaic for somatic NLRP3 mutations. Such patients also respond dramatically to IL-1 inhibition. Similarly, somatic mosaicism in NLRP3 has been found in Schnitzler's syndrome, which presents in middle age with recurrent fever, urticarial rash, elevated acute phase reactants, monoclonal IgM gammopathy, and abnormal bone remodeling. IL-1 inhibition is the treatment of choice for Schnitzler's syndrome.

OTHER INHERITED AUTOINFLAMMATORY DISEASES

There are a number of other Mendelian autoinflammatory diseases in which recurrent fevers are not a prominent clinical sign but that involve abnormalities of innate immunity. The syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) is a dominantly inherited disorder that presents with episodes of sterile pyogenic monoarthritis often induced by trauma, severe pyoderma gangrenosum, and severe cystic acne, usually beginning in puberty. It is caused by mutations in PSTPIP1, which encodes a pyrin-binding protein, and the arthritic manifestations often respond to IL-1 inhibition. Patients with the recessively inherited deficiency of the IL-1 receptor antagonist (DIRA) present with a generalized pustular rash and multifocal sterile osteomyelitis, and show dramatic clinical responses to anakinra, the recombinant form of the protein they lack. IL-36 is another member of the IL-1 family of cytokines that is regulated by an endogenous receptor antagonist. The recessively inherited deficiency of the IL-36 receptor antagonist (DITRA) presents with episodes of generalized pustular psoriasis and dramatic systemic inflammation.

Whereas PAPA, DIRA, and DITRA all involve mutations in IL-1-related molecules, other autoinflammatory diseases are caused by mutations in other components of innate immunity. Blau's syndrome is caused by mutations in CARD15 (also known as NOD2), which regulates nuclear factor-κB activation. Blau's syndrome is characterized by granulomatous dermatitis, uveitis, and arthritis; distinct CARD15 variants predispose to Crohn's disease. Recessive mutations in one or more

components of the proteasome lead to excessive interferon signaling and the syndrome of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), a severe form of generalized panniculitis.

De novo gain-of-function mutations in TMEM173, encoding the stimulator of interferon genes (STING), cause severe vasculopathy and pulmonary fibrosis. Recessive loss-of-function mutations in CERCR1, encoding adenosine deaminase 2 (ADA2), cause a vasculopathy that can manifest as livedoid rash, early-onset lacunar strokes, or polyarteritis nodosa.

Finally, it should be noted that a number of common, genetically complex disorders are now sometimes considered autoinflammatory, because of evidence that components of the innate immune system, such as the inflammasome, may play a role in the pathogenesis. Two prominent examples are gout and atherosclerosis. Large clinical trials of IL-1 inhibitors have been initiated in both conditions.

CHAPTER 17

POLYMYOSITIS, DERMATOMYOSITIS, AND INCLUSION BODY MYOSITIS

Marinos C. Dalakas

The inflammatory myopathies represent the largest group of acquired and potentially treatable causes of skeletal muscle weakness. They are classified into three major groups: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM).

CLINICAL FEATURES

The prevalence of the inflammatory myopathies is estimated at 1 in 100,000. PM as a stand-alone entity is a rare disease. DM affects both children and adults and women more often than men. IBM is three times more frequent in men than in women, more common in whites than blacks, and is most likely to affect persons age >50 years.

These disorders present as progressive and symmetric muscle weakness except for IBM, which can have an asymmetric pattern. Patients usually report increasing difficulty with everyday tasks requiring the use of proximal muscles, such as getting up from a chair, climbing steps, stepping onto a curb, lifting objects, or combing hair. Fine-motor movements that depend on the strength of distal muscles, such as buttoning a shirt, sewing, knitting, or writing, are affected only late in the course of PM and DM, but fairly early in IBM. Falling is common in IBM because of early involvement of the quadriceps muscle, with buckling of the knees. Ocular muscles are spared, even in advanced, untreated cases; if these muscles are affected, the diagnosis of inflammatory myopathy should be questioned. Facial muscles are unaffected in PM and DM, but mild facial muscle weakness is common in patients with IBM. In all forms of inflammatory myopathy, pharyngeal and neck-flexor muscles are often involved, causing dysphagia or difficulty in holding up the head (head drop). In advanced and rarely in acute cases, respiratory muscles may also be affected. Severe weakness, if untreated, is almost always associated with muscle wasting. Sensation remains normal. The tendon reflexes are preserved but may be absent in severely weakened or atrophied muscles, especially in IBM, where atrophy of the quadriceps and the distal muscles is common. Myalgia and muscle tenderness may occur in a small number of patients, usually early in the disease, and particularly in DM associated with connective tissue disorders. Weakness in PM and DM progresses subacutely over a period of weeks or months and rarely acutely; by contrast, IBM progresses very slowly, over years, simulating a late-life muscular dystrophy or slowly progressive motor neuron disorder.

SPECIFIC FEATURES

(Table 17-1)

Polymyositis

The actual onset of PM is often not easily determined, and patients typically delay seeking medical advice for several weeks or even months. This is in contrast to DM, in which the rash facilitates early recognition (see below). PM mimics many other myopathies and is a diagnosis of exclusion. It is a subacute inflammatory myopathy affecting adults, and rarely children, who do not have any of the following: rash, involvement of the extraocular and facial muscles, family history of a neuromuscular disease, history of exposure to myotoxic drugs or toxins, endocrinopathy, neurogenic disease, muscular dystrophy, biochemical muscle disorder (deficiency of a muscle enzyme), or IBM as excluded by muscle biopsy analysis (see below). As an isolated entity, PM is a rare (and overdiagnosed) disorder; more commonly, PM occurs in association with a systemic autoimmune or connective tissue disease or

TABLE 17-1

FEATURES ASSOCIATED WITH INFLAMMATORY MYOPATHIES

CHARACTERISTIC	POLYMYOSITIS	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Age at onset	>18 years	Adulthood and childhood	>50 years
Familial association	No	No	Yes, in some rare cases
Extramuscular manifestations	Yes	Yes	Yes
Associated conditions			
Connective tissue diseases	Yes[a]	Scleroderma and mixed connective tissue disease (overlap syndromes)	Yes, in up to 20% of cases[a]
Systemic autoimmune diseases[b]	Frequent	Infrequent	Infrequent
Malignancy	No	Yes, in up to 15% of cases	No
Viruses	Yes[c]	Unproven	Yes[c]
Drugs[d]	Yes	Yes, rarely	No
Parasites and bacteria[e]	Yes	No	No

[a]Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic sclerosis, mixed connective tissue disease.
[b]Crohn's disease, vasculitis, sarcoidosis, primary biliary cirrhosis, adult celiac disease, chronic graft-versus-host disease, discoid lupus, ankylosing spondylitis, Behçet's syndrome, myasthenia gravis, acne fulminans, dermatitis herpetiformis, psoriasis, Hashimoto's disease, granulomatous diseases, agammaglobulinemia, monoclonal gammopathy, hypereosinophilic syndrome, Lyme disease, Kawasaki disease, autoimmune thrombocytopenia, hypergammaglobulinemic purpura, hereditary complement deficiency, IgA deficiency.
[c]HIV (human immunodeficiency virus) and HTLV-1 (human T cell lymphotropic virus type 1).
[d]Drugs include penicillamine (dermatomyositis and polymyositis), zidovudine (polymyositis), statins (necrotizing, toxic, or autoimmune myositis), and contaminated tryptophan (dermatomyositis-like illness). Other myotoxic drugs may cause myopathy but not an inflammatory myopathy (see text for details).
[e]Parasites (protozoa, cestodes, nematodes), tropical and bacterial myositis (pyomyositis).

with a known viral or bacterial infection. Drugs, especially D-penicillamine, statins, or zidovudine (AZT), may also trigger an inflammatory myopathy similar to PM.

Dermatomyositis

DM is a distinctive entity identified by a characteristic rash accompanying, or more often preceding, muscle weakness. The rash may consist of a blue-purple discoloration on the upper eyelids with edema (heliotrope rash), a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron's sign). The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a V sign), or back and shoulders (shawl sign), and may worsen after sun exposure. In some patients, the rash is pruritic, especially on the scalp, chest, and back. Dilated capillary loops at the base of the fingernails are also characteristic. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling mechanic's hands. The weakness can be mild, moderate, or severe enough to lead to quadriparesis. At times, the muscle strength appears normal, hence the term dermatomyositis sine myositis. When muscle biopsy is performed in such cases, however, significant perivascular and perimysial inflammation is often seen.

DM usually occurs alone but may overlap with scleroderma and mixed connective tissue disease. Fasciitis and thickening of the skin, similar to that seen in chronic cases of DM, have occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated l-tryptophan.

Inclusion body myositis

In patients ≥50 years of age, IBM is the most common of the inflammatory myopathies. It is often misdiagnosed as PM and is suspected only later when a patient with presumed PM does not respond to therapy. Weakness and atrophy of the distal muscles, especially foot extensors and deep finger flexors, occur in almost all cases of IBM and may be a clue to early diagnosis. Some patients present with falls because their knees collapse due to early quadriceps weakness. Others present with weakness in the small muscles of the hands, especially finger flexors, and complain of inability to hold objects such as golf clubs or perform tasks such as turning keys or tying knots. On occasion, the weakness and accompanying atrophy can be asymmetric and selectively involve the quadriceps, iliopsoas, triceps, biceps, and finger flexors, resembling a lower motor neuron disease. Dysphagia is common, occurring in up to 60% of IBM patients, and may lead to episodes of choking. Sensory examination is generally normal; some patients have mildly diminished vibratory sensation at the ankles that presumably is age-related. The pattern of distal

weakness, which superficially resembles motor neuron or peripheral nerve disease, results from the myopathic process affecting distal muscles selectively. Disease progression is slow but steady, and most patients require an assistive device such as cane, walker, or wheelchair within several years of onset.

In at least 20% of cases, IBM is associated with systemic autoimmune or connective tissue diseases. Familial aggregation of typical IBM may occur; such cases have been designated as *f*amilial in*fl*ammatory IBM. T is disorder is distinct from hereditary inclusion body myopathy (h-IBM), which describes a heterogeneous group of recessive, and less frequently dominant, inherited syndromes; the h-IBMs are noninflammatory myopathies. A subset of h-IBM that spares the quadriceps muscles has emerged as a distinct entity. T is disorder, originally described in Iranian Jews and now seen in many ethnic groups, is linked to chromosome 9p1 and results from mutations in the UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) gene.

ASSOCIATED CLINICAL FINDINGS

Extramuscular manifestations

T ese may be present to a varying degree in patients with PM or DM, and include:

1. Systemic symptoms, such as fever, malaise, weight loss, arthralgia, and Raynaud's phenomenon, especially when inflammatory myopathy is associated with a connective tissue disorder.
2. Joint contractures, mostly in DM and especially in children.
3. Dysphagia and gastrointestinal symptoms, due to involvement of oropharyngeal striated muscles and upper esophagus, especially in DM and IBM.
4. Cardiac disturbances, including atrioventricular conduction defects, tachyarrhythmias, dilated cardiomyopathy, a low ejection fraction, and congestive heart failure, which may rarely occur either from the disease itself or from hypertension associated with long-term use of glucocorticoids.
5. Pulmonary dys*f*unction, due to weakness of the thoracic muscles, interstitial lung disease, or drug-induced pneumonitis (e.g., from methotrexate), which may cause dyspnea, nonproductive cough, and aspiration pneumonia. Interstitial lung disease may precede myopathy or occur early in the disease and develops in up to 10% of patients with PM or DM, most of whom have antibodies to t-RNA synthetases, as described below.
6. Subcutaneous calci cations, in DM, sometimes extruding on the skin and causing ulcerations and infections.
7. Arthralgias, synovitis, or deforming arthropathy with subluxation in the interphalangeal joints, which can occur in some patients with DM and PM who have Jo-1 antibodies (see below).

Association with malignancies

Although all the inflammatory myopathies can have a chance association with malignant lesions, especially in older age groups, the incidence of malignant conditions appears to be specifically increased only in patients with DM and not in those with PM or IBM. T e most common tumors associated with DM are ovarian cancer, breast cancer, melanoma, colon cancer, and non-Hodgkin's lymphoma. T e extent of the search that should be conducted for an occult neoplasm in adults with DM depends on the clinical circumstances. Tumors in these patients are usually uncovered by abnormal findings in the medical history and physical examination and not through an extensive blind search. T e weight of evidence argues against performing expensive, invasive, and nondirected tumor searches. A complete annual physical examination with pelvic, breast (mammogram, if indicated), and rectal examinations (with colonoscopy according to age and family history); urinalysis; complete blood count; blood chemistry tests; and a chest film should suf ce in most cases. In Asians, nasopharyngeal cancer is common, and a careful examination of ears, nose, and throat is indicated. If malignancy is clinically suspected, screening with a whole-body positron emission tomography (PET) scan should be considered.

Overlap syndromes

T ese describe the association of inflammatory myopathies with connective tissue diseases. A well-characterized overlap syndrome occurs in patients with DM who also have manifestations of systemic sclerosis or mixed connective tissue disease, such as sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits (Table 17-1). By contrast, signs of rheumatoid arthritis, systemic lupus erythematosus, or Sjögren's syndrome are very rare in patients with DM. Patients with the overlap syndrome of DM and systemic sclerosis may have a specific antinuclear antibody, the anti-PM/Scl, directed against a nucleolar-protein complex.

PATHOGENESIS

An autoimmune etiology of the inflammatory myopathies is indirectly supported by an association with other autoimmune or connective tissue diseases; the presence of various autoantibodies; an association with

specific major histocompatibility complex (MHC) genes; demonstration of T cell–mediated myocytotoxicity or complement-mediated microangiopathy; and a response to immunotherapy.

Autoantibodies and immunogenetics

Various autoantibodies against nuclear antigens (antinuclear antibodies) and cytoplasmic antigens are found in up to 30% of patients with inflammatory myopathies. T e antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti-signal-recognition particles). T e antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with anti-Jo-1 antibodies have interstitial lung disease. Some patients with the anti-Jo-1 antibody also have Raynaud's phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. DR3 haplotypes (molecular designation DRB1*0301, DQB1*0201) occur in up to 75% of patients with PM and IBM, whereas in juvenile DM, there is an increased frequency of DQA1*0501 **(Chap. 2)**. Antibodies against the cytosolic 5′-nucleotidase 1A, an enzyme abundantly expressed in muscle and thought to be involved in DNA degradation and repair, have been detected in one-third of IBM patients. Although the pathogenic significance of these antibodies is still unknown, they highlight the presence of an immune response, as discussed below.

Immunopathologic mechanisms

In DM, humoral immune mechanisms are implicated, resulting in a microangiopathy and muscle ischemia **(Fig. 17-1)**. Endomysial inflammatory infiltrates are composed of B cells located in proximity to CD4 T cells,

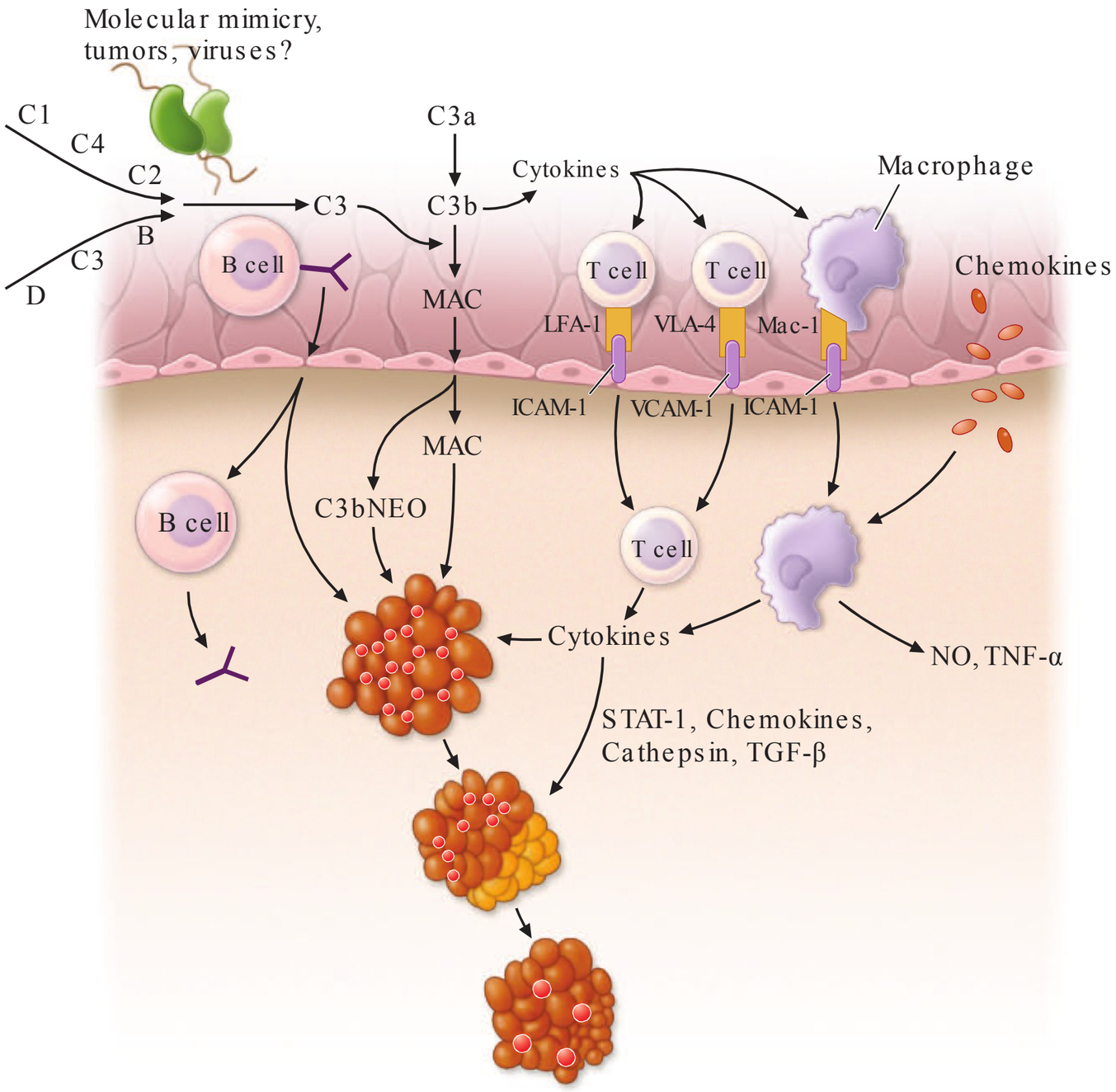


FIGURE 17-1

Immunopathogenesis of dermatomyositis. Activation of complement, possibly by autoantibodies (Y), against endothelial cells and formation of C3 via the classic or alternative pathway. Activated C3 leads to formation of C3b, C3bNEO, and membrane attack complexes (MAC), which are deposited in and around the endothelial cell wall of the endomysial capillaries. Deposition of MAC leads to destruction of capillaries, ischemia, or microinfarcts, most prominent in the periphery of the fascicles, and perifascicular atrophy. B cells, plasmacytoid dendritic cells, CD4 T cells, and macrophages traffic from the circulation to the muscle. Endothelial expression of vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) is induced by cytokines released by the mononuclear cells. Integrins, specifically very late activation antigen (VLA)-4 and lymphocyte function–associated antigen (LFA)-1, bind VCAM and ICAM and promote T cell and macrophage infiltration of muscle through the endothelial cell wall.

plasmacytoid dendritic cells, and macrophages; there is a relative absence of lymphocytic invasion of nonnecrotic muscle fibers. Activation of the complement C5b-9 membranolytic attack complex is thought to be a critical early event that triggers release of proinflammatory cytokines and chemokines, induces expression of vascular cell adhesion molecule (VCAM) 1 and intercellular adhesion molecule (ICAM) 1 on endothelial cells, and facilitates migration of activated lymphoid cells to the perimysial and endomysial spaces. Necrosis of the endothelial cells, reduced numbers of endomysial capillaries, ischemia, and muscle-fiber destruction resembling microinfarcts occur. T e remaining capillaries often have dilated lumens in response to the ischemic process. Larger intramuscular blood vessels may also be affected in the same pattern. Residual perifascicular atrophy reflects the endofascicular hypoperfusion that is prominent in the periphery of muscle fascicles. Increased expression of type I interferon–inducible proteins is also noted in these regions.

By contrast, in PM and IBM, a mechanism of T cell–mediated cytotoxicity is likely. CD8 T cells, along with macrophages, initially surround and eventually invade and destroy healthy, nonnecrotic muscle fibers that aberrantly express class I MHC molecules. MHC-I expression, absent from the sarcolemma of normal muscle fibers, is probably induced by cytokines secreted by activated T cells and macrophages. T e CD8/MHC-I complex is characteristic of PM and IBM; its detection can aid in confirming the histologic diagnosis of PM, as discussed below. T e cytotoxic CD8 T cells contain perforin and granzyme granules directed toward the surface of the muscle fibers and capable of inducing myonecrosis. Analysis of T cell receptor molecules expressed by the infiltrating CD8 cells has revealed clonal expansion and conserved sequences in the antigen-binding region, both suggesting an antigen-driven T cell response. Whether the putative antigens are endogenous (e.g., muscle) or exogenous (e.g., viral) sequences is unknown. Viruses have not been identified within the muscle fibers. Costimulatory molecules and their counterreceptors, which are fundamental for T cell activation and antigen recognition, are strongly upregulated in PM and IBM. As noted above, the possibility that B cells and the humoral immune system might also play a role in IBM is suggested by the identification of anti-cytosolic 5′-nucleotidase 1A antibodies in some patients. Key molecules involved in T cell–mediated cytotoxicity are depicted in **Fig. 17-2**.

The role of nonimmune factors in IBM

In IBM, the presence of Congo red–positive amyloid deposits within some vacuolated muscle fibers and abnormal mitochondria with cytochrome oxidase–negative fibers suggest that, in addition to the autoimmune component, there is also a degenerative process. Similar to Alzheimer's disease, the intracellular amyloid deposits in IBM are immunoreactive against amyloid precursor protein (APP), β-amyloid, chymotrypsin, apolipoprotein E, presenilin, ubiquitin, and phosphorylated tau, but it is unclear whether these deposits, which are also seen in other vacuolar myopathies, are directly pathogenic or represent secondary phenomena. T e same is true for the mitochondrial abnormalities, which may also be secondary to the effects of aging or a bystander effect of upregulated cytokines. Expression of cytokines and upregulation of MHC class I by the muscle fibers may cause an endoplasmic reticulum stress response resulting in intracellular accumulation of stressor molecules or misfolded glycoproteins and activation of nuclear factor κB (NF-κB), leading to further cytokine activation.

Association with viral infections and the role of retroviruses

Several viruses, including coxsackieviruses, influenza, paramyxoviruses, mumps, cytomegalovirus, and Epstein-Barr virus, have been indirectly associated with myositis. For the coxsackieviruses, an autoimmune myositis triggered by molecular mimicry has been proposed because of structural homology between histidyl-transfer RNA synthetase that is the target of the Jo-1 antibody (see above) and genomic RNA of an animal picornavirus, the encephalomyocarditis virus. Sensitive polymerase chain reaction (PCR) studies, however, have repeatedly failed to confirm the presence of such viruses in muscle biopsies.

T e best evidence of a viral connection in PM and IBM is with the retroviruses. Some individuals infected with HIV or with human T cell lymphotropic virus 1 (HTLV-1) develop PM or IBM; a similar disorder has been described in nonhuman primates infected with the simian immunodeficiency virus. T e inflammatory myopathy may occur as the initial manifestation of a retroviral infection, or myositis may develop later in the disease course. Retroviral antigens have been detected only in occasional endomysial macrophages and not within the muscle fibers themselves, suggesting that persistent infection and viral replication within the muscle does not occur. Histologic findings are identical to retroviral-negative PM or IBM. T e infiltrating T cells in the muscle have a clonal bias and a number of them are retroviral-specific. T is disorder should be distinguished from a toxic myopathy related to long-term therapy with AZT, characterized by fatigue, myalgia, mild muscle weakness, and mild elevation of creatine kinase (CK). AZT-induced myopathy, which generally improves when the drug is discontinued, is a mitochondrial disorder characterized histologically by

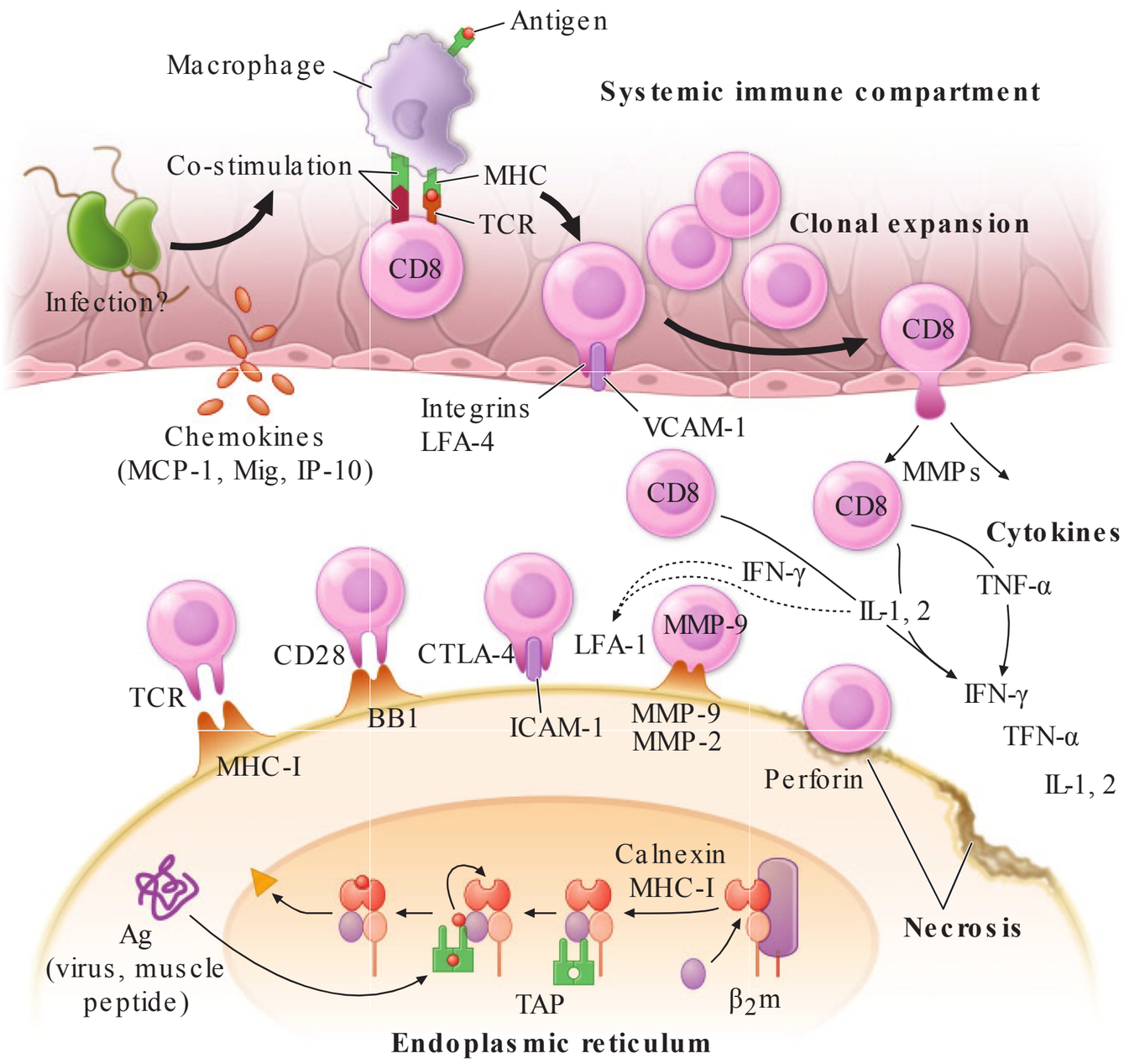


FIGURE 17-2
Cell-mediated mechanisms of muscle damage in polymyositis (PM) and inclusion body myositis (IBM). Antigen-specific CD8 cells are expanded in the periphery, cross the endothelial barrier, and bind directly to muscle fibers via T cell receptor (TCR) molecules that recognize aberrantly expressed major histocompatibility complex (MHC)-I. Engagement of co-stimulatory molecules (BB1 and ICOSL) with their ligands (CD28, CTLA-4, and ICOS), along with ICAM-1/LFA-1, stabilize the CD8–muscle fiber interaction. Metalloproteinases (MMPs) facilitate the migration of T cells and their attachment to the muscle surface. Muscle fiber necrosis occurs via perforin granules released by the autoaggressive T cells. A direct myocytotoxic effect exerted by the cytokines interferon (IFN) γ, interleukin (IL) 1, or tumor necrosis factor (TNF) α may also play a role. Death of the muscle fiber is mediated by necrosis. MHC class I molecules consist of a heavy chain and a light chain (β_2 microglobulin [β_2m]) complexed with an antigenic peptide that is transported into the endoplasmic reticulum by TAP proteins (Chap. 2).

"ragged-red" fibers. AZT inhibits γ-DNA polymerase, an enzyme found solely in the mitochondrial matrix.

GLOBAL ISSUES



Inadequate data exist with respect to possible differences in the prevalence of the inflammatory myopathies in various parts of the world. PM appears to be reported more often in Asia and southern Europe, whereas IBM seems to be more frequently recognized in North America, northern Europe, and Australia. Whether this represents differences in diagnostic methods and disease awareness or true disease prevalence remains unclear. Pyomyositis and parasitic myositis are clearly more common in the tropics, whereas HIV-associated PM and IBM are more commonly encountered in areas endemic for HIV. In patients from Asia, nasopharyngeal cancer appears to be a malignancy more commonly associated with DM, necessitating the need to specifically search for these tumors in this population.

DIFFERENTIAL DIAGNOSIS

The clinical picture of the typical skin rash and proximal or diffuse muscle weakness has few causes other than DM. However, proximal muscle weakness without skin involvement can be due to many conditions other than PM or IBM.

Subacute or chronic progressive muscle weakness

This may be due to denervating conditions such as the spinal muscular atrophies or amyotrophic lateral sclerosis. In addition to the muscle weakness, upper motor neuron signs in the latter and signs of denervation detected by electromyography (EMG) aid in the diagnosis. The muscular dystrophies may be additional considerations; however, these disorders usually develop over years rather than weeks or months and rarely present after the age of 30 years.

It may be dif cult, even with a muscle biopsy, to distinguish chronic PM from a rapidly advancing muscular dystrophy. T is is particularly true of facioscapulohumeral muscular dystrophy, dysferlin myopathy, and the dystrophinopathies where inflammatory cell infiltration is often found early in the disease. Such doubtful cases should always be given an adequate trial of glucocorticoid therapy and undergo genetic testing to exclude muscular dystrophy. Identification of the MHC/CD8 lesion by muscle biopsy is helpful to identify cases of PM. Some metabolic myopathies, including glycogen storage disease due to myophosphorylase or acid maltase deficiency, lipid storage myopathies due to carnitine deficiency, and mitochondrial diseases produce weakness that is often associated with other characteristic clinical signs; diagnosis rests upon histochemical and biochemical studies of the muscle biopsy. T e endocrine myopathies such as those due to hypercorticosteroidism, hyper- and hypothyroidism, and hyper- and hypoparathyroidism require the appropriate laboratory investigations for diagnosis. Muscle wasting in patients with an underlying neoplasm may be due to disuse, cachexia, or rarely a paraneoplastic neuromyopathy.

Diseases of the neuromuscular junction, including myasthenia gravis or the Lambert-Eaton myasthenic syndrome, cause fatiguing weakness that also affects ocular and other cranial muscles. Repetitive nerve stimulation and single-fiber EMG studies aid in diagnosis.

Acute muscle weakness

T is may be caused by an acute neuropathy such as Guillain-Barré syndrome, transverse myelitis, a neurotoxin, or a neurotropic viral infection such as poliomyelitis or West Nile virus. When acute weakness is associated with very high levels of serum CK (often in the thousands), painful muscle cramps, rhabdomyolysis, and myoglobinuria, it may be due to a necrotizing autoimmune myositis, as discussed below, a viral infection or a metabolic disorder such as myophosphorylase deficiency, or carnitine palmitoyltransferase deficiency. Several animal parasites, including protozoa (Toxoplasma, Trypanosoma), cestodes (cysticerci), and nematodes (trichinae), may produce a focal or diffuse inflammatory myopathy known as parasitic polymyositis. Staphylococcus aureus, Yersinia, Streptococcus, or anaerobic bacteria may produce a suppurative myositis, known as tropical polymyositis, or pyomyositis. Pyomyositis, previously rare in the west, is now occasionally seen in AIDS patients. Other bacteria, such as Borrelia burgdor*f*eri (Lyme disease) and Legionella pneumophila (Legionnaire's disease), may infrequently cause myositis.

Patients with periodic paralysis experience recurrent episodes of acute muscle weakness without pain, always beginning in childhood. Chronic alcoholics may develop painful myopathy with myoglobinuria after a bout of heavy drinking. Acute painless muscle weakness with myoglobinuria may occur with prolonged hypokalemia, or hypophosphatemia and hypomagnesemia, usually in chronic alcoholics or in patients on nasogastric suction receiving parenteral hyperalimentation.

Myo*f*asciitis

T is distinctive inflammatory disorder affecting muscle and fascia presents as diffuse myalgias, skin induration, fatigue, and mild muscle weakness; mild elevations of serum CK are usually present. T e most common form is eosinophilic myofasciitis characterized by peripheral blood eosinophilia and eosinophilic infiltrates in the endomysial tissue. In some patients, the eosinophilic myositis/fasciitis occurs in the context of parasitic infections, vasculitis, mixed connective tissue disease, hypereosinophilic syndrome, or toxic exposures (e.g., toxic oil syndrome, contaminated l-tryptophan) or with mutations in the calpain gene. A distinct subset of myofasciitis is characterized by pronounced infiltration of the connective tissue around the muscle by sheets of periodic acid–Schiff-positive macrophages and occasional CD8 T cells (macrophagic myofasciitis or inflammatory myositis with abundant macrophages [IMAM]). A focal form of this disorder, limited to sites of previous vaccinations, administered months or years earlier, has been linked to an aluminum-containing substrate in vaccines. T is disorder, which to date has not been observed outside of France, responds to glucocorticoid therapy, and the overall prognosis seems favorable.

Necrotizing autoimmune myositis

T is is an increasingly recognized entity that has distinct features, even though it is often labeled as PM. It presents as an acute or subacute onset of symmetric muscle weakness; CK is typically extremely high. T e weakness can be severe. Coexisting interstitial lung disease and cardiomyopathy may be present. T e disorder may develop after a viral infection, in association with cancer, or in patients taking statins when the myopathy continues to worsen after statin withdrawal. Some patients have antibodies against signal recognition particle (SRP) or against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a 100-kDa protein considered the pharmacologic target of statins. T e muscle biopsy demonstrates necrotic fibers infiltrated by macrophages but only rare, if any, T cell infiltrates. Muscle MHC-I expression is only slightly and focally upregulated. T e capillaries may be swollen with hyalinization, thickening of the capillary wall, and deposition of complement. Most patients respond to immunotherapy, but some are resistant.

Hyperacute necrotizing fasciitis/myositis (flesh-eating disease)

This is a fulminant infectious disease, seen most often in the tropics or in conditions with poor hygiene, characterized by widespread necrosis of the superficial fascia and muscle of a limb; if the scrotum, perineum, and abdominal wall are affected, the condition is referred to as Fournier's gangrene. It may be caused by group A β-hemolytic Streptococcus, methicillin-sensitive S. aureus, Pseudomonas aeruginosa, Vibrio vulnificus, clostridial species (gas gangrene), or polymicrobial infection with anaerobes and facultative bacteria; toxins from these bacteria may act as superantigens **(Chap. 1)**. The port of bacterial entry is usually a trivial cut or skin abrasion, and the source is contact with carriers of the organism. Individuals with diabetes mellitus, immunodeficiency states, or systemic illnesses such as liver failure are most susceptible. Systemic varicella is a predisposing factor in children.

The disease presents with swelling, pain, and redness in the involved area followed by a rapid tissue necrosis of fascia and muscle that progresses at an estimated rate of 3 cm/h. Emergency debridement, antibiotics, IV immunoglobulin (IVIg), and even hyperbaric oxygen have been recommended. In progressive or advanced cases, amputation of the affected limb may be necessary to avoid a fatal outcome.

Drug-induced myopathies

d-Penicillamine, procainamide, and statins may produce a true myositis resembling PM or necrotizing myositis. A DM-like illness has been associated with the contaminated preparations of l-tryptophan. As noted above, AZT causes a mitochondrial myopathy. Other drugs may elicit a toxic noninflammatory myopathy that is histologically different from DM, PM, or IBM. These include cholesterol-lowering agents such as clofibrate, lovastatin, simvastatin, or pravastatin, especially when combined with cyclosporine, amiodarone, or gemfibrozil. Mild statin-induced myopathic symptoms (such as myalgia, fatigue, or asymptomatic elevations of CK) are self-limited and usually improve after discontinuation of the drug. In rare patients, however, muscle weakness continues to progress even after the statin is withdrawn; in these cases, a diagnostic muscle biopsy is indicated and search for antibodies to HMGCR is suggested; if histologic evidence of PM or necrotizing myositis is present, immunotherapy should be initiated. Rhabdomyolysis and myoglobinuria have been rarely associated with amphotericin B, ε-aminocaproic acid, fenfluramine, heroin, and phencyclidine. The use of amiodarone, chloroquine, colchicine, carbimazole, emetine, etretinate, and ipecac syrup; chronic laxative or licorice use resulting in hypokalemia; and glucocorticoid or growth hormone administration have also been associated with myopathic muscle weakness. Some neuromuscular blocking agents such as pancuronium, in combination with glucocorticoids, may cause an acute critical illness myopathy. A careful drug history is essential for diagnosis of these drug-induced myopathies, which do not require immunosuppressive therapy except when an autoimmune myopathy has been triggered, as noted above.

"Weakness" due to muscle pain and muscle tenderness

A number of conditions including polymyalgia rheumatica **(Chap. 11)** and arthritic disorders of adjacent joints may enter into the differential diagnosis of inflammatory myopathy, even though they do not cause myositis. The muscle biopsy is either normal or discloses type II muscle fiber atrophy. Patients with fibromyalgia **(Chap. 22)** complain of focal or diffuse muscle tenderness, fatigue, and aching, which is sometimes poorly differentiated from joint pain. Some patients, however, have muscle tenderness, painful muscles on movement, and signs suggestive of a collagen vascular disorder, such as an increased erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, or rheumatoid factor, along with modest elevation of the serum CK and aldolase. They demonstrate a "break-away" pattern of weakness with difficulty sustaining effort but not true muscle weakness. The muscle biopsy is usually normal or nonspecific. Many such patients show some response to nonsteroidal anti-inflammatory agents or glucocorticoids, although most continue to have indolent complaints. An indolent fasciitis in the setting of an ill-defined connective tissue disorder may be at times present, and these patients should not be labeled as having a psychosomatic disorder. Chronic *f*atigue syndrome, which may follow a viral infection, can present with debilitating fatigue, sore throat, painful lymphadenopathy, myalgia, arthralgia, sleep disorder, and headache. These patients do not have muscle weakness, and the muscle biopsy is normal.

DIAGNOSIS

The clinically suspected diagnosis of PM, DM, IBM, or necrotizing myositis is confirmed by analysis of serum muscle enzymes, EMG findings, and muscle biopsy **(Table 17-2)**.

The most sensitive enzyme is CK, which in active disease can be elevated as much as 50-fold. Although the CK level usually parallels disease activity, it can be normal in some patients with active IBM or DM, especially when associated with a connective tissue disease. The CK is always elevated in patients with active PM. Along with the CK, the serum glutamic-oxaloacetic and

TABLE 17-2

CRITERIA FOR DIAGNOSIS OF INFLAMMATORY MYOPATHIES

	POLYMYOSITIS			
CRITERION	DEFINITE	PROBABLE	DERMATOMYOSITIS	INCLUSION BODY MYOSITIS
Myopathic muscle weakness[a]	Yes	Yes	Yes[b]	Yes; slow onset, early involvement of distal muscles, frequent falls
Electromyographic findings	Myopathic	Myopathic	Myopathic	Myopathic with mixed potentials
Muscle enzymes	Elevated (up to 50-fold)	Elevated (up to 50-fold)	Elevated (up to 50-fold) or normal	Elevated (up to 10-fold) or normal
Muscle biopsy findings[c]	"Primary" inflammation with the CD8/MHC-I complex and no vacuoles	Ubiquitous MHC-I expression but minimal inflammation and no vacuoles[d]	Perifascicular, perimysial, or perivascular infiltrates, perifascicular atrophy	Primary inflammation with CD8/MHC-I complex; vacuolated fibers with β-amyloid deposits; cytochrome oxygenase–negative fibers; signs of chronic myopathy[e]
Rash or calcinosis	Absent	Absent	Present[f]	Absent

[a]Myopathic muscle weakness, af ecting proximal muscles more than distal ones and sparing eye and facial muscles, is characterized by a subacute onset (weeks to months) and rapid progression in patients who have no family history of neuromuscular disease, no endocrinopathy, no exposure to myotoxic drugs or toxins, and no biochemical muscle disease (excluded on the basis of muscle biopsy findings).
[b]In some cases with the typical rash, the muscle strength is seemingly normal (dermatomyositis sine myositis); these patients often have new onset of easy fatigue and reduced endurance. Careful muscle testing may reveal mild muscle weakness.
[c]See text for details.
[d]An adequate trial of prednisone or other immunosuppressive drugs is warranted in probable cases. If, in retrospect, the disease is unresponsive to therapy, another muscle biopsy should be considered to exclude other diseases or possible evolution in inclusion body myositis.
[e]If the muscle biopsy does not contain vacuolated fibers but shows chronic myopathy with hypertrophic fibers, primary inflammation with the CD8/MHC-I complex, and cytochrome oxygenase–negative fibers, the diagnosis is probable inclusion body myositis.
[f]If rash is absent but muscle biopsy findings are characteristic of dermatomyositis, the diagnosis is probable dermatomyositis.

glutamate pyruvate transaminases, lactate dehydrogenase, and aldolase may be elevated.

Needle EMG shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed potentials (polyphasic units of short and long duration) indicating a chronic process and muscle fiber regeneration are often present in IBM. T ese EMG findings are not diagnostic of an inflammatory myopathy but are useful to identify the presence of active or chronic myopathy and to exclude neurogenic disorders.

Magnetic resonance imaging (MRI) is not routinely used for the diagnosis of PM, DM, or IBM. However, it may provide information or guide the location of the muscle biopsy in certain clinical settings.

Muscle biopsy—despite occasional variability in demonstrating all of the typical pathologic findings—is the most sensitive and specific test for establishing the diagnosis of inflammatory myopathy and for excluding other neuromuscular diseases. Inflammation is the histologic hallmark for these diseases; however, additional features are characteristic of each subtype **(Figs. 17-3, 17-4,** and **17-5).**

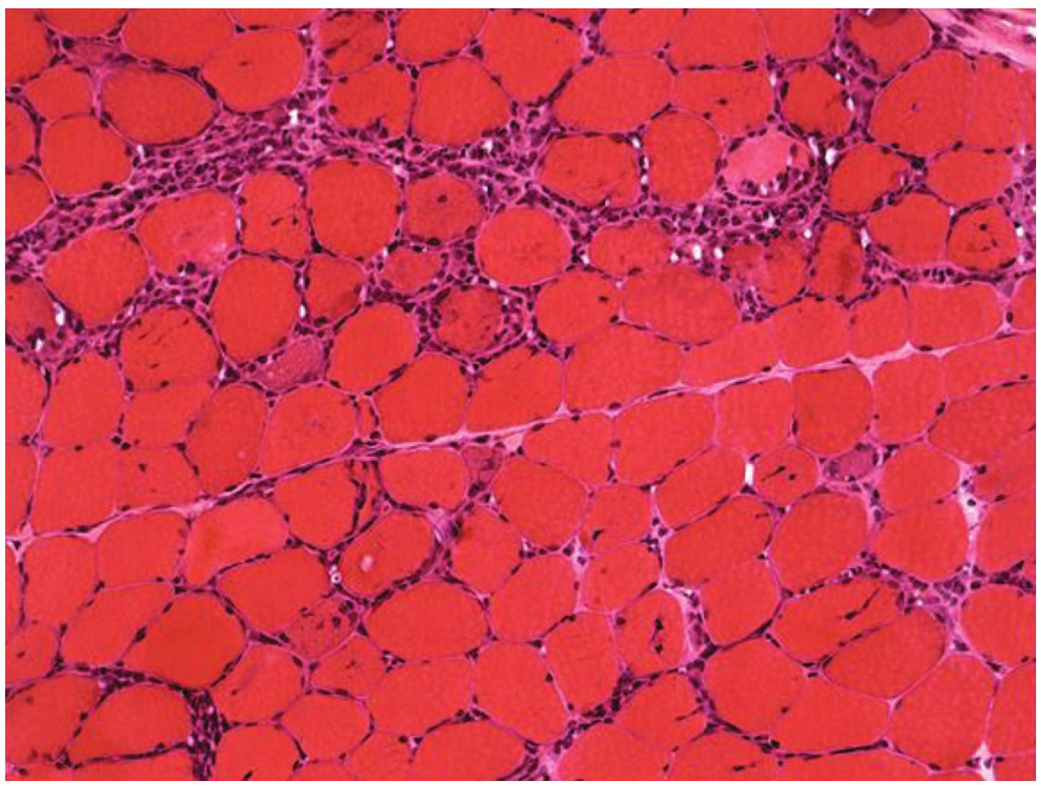


FIGURE 17-3
Cross-section of a muscle biopsy from a patient with polymyositis demonstrates scattered inflammatory foci with lymphocytes invading or surrounding muscle fibers. Note lack of chronic myopathic features (increased connective tissue, atrophic or hypertrophic fibers) as seen in inclusion body myositis.

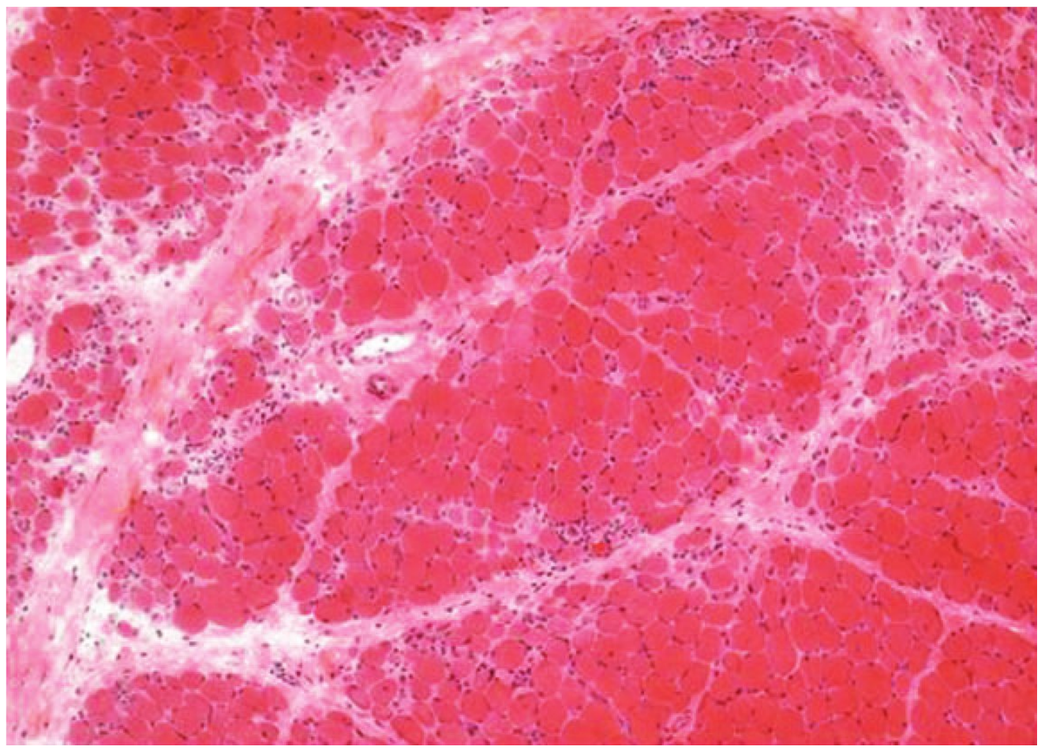


FIGURE 17-4
Cross-section of a muscle biopsy from a patient with dermatomyositis demonstrates atrophy of the fibers at the periphery of the fascicle (perifascicular atrophy).

In PM the inflammation is primary, a term used to indicate that the inflammation is not reactive and the T cell infiltrates, located primarily within the muscle fascicles (endomysially), surround individual, healthy muscle fibers and result in phagocytosis and necrosis (Fig. 17-3). T e MHC-I molecule is ubiquitously expressed on the sarcolemma, even in fibers not invaded by CD8+ cells. T e CD8/MHC-I lesion is characteristic and useful to confirm or establish the diagnosis and to exclude disorders with secondary, nonspecific, inflammation, such as in some muscular dystrophies. When the disease is chronic, connective tissue is increased and may react positively with alkaline phosphatase. In necrotizing myositis, there are abundant necrotic fibers invaded or surrounded by macrophages, but no lymphocytic infiltrates or MHC-I expression beyond the necrotic fibers.

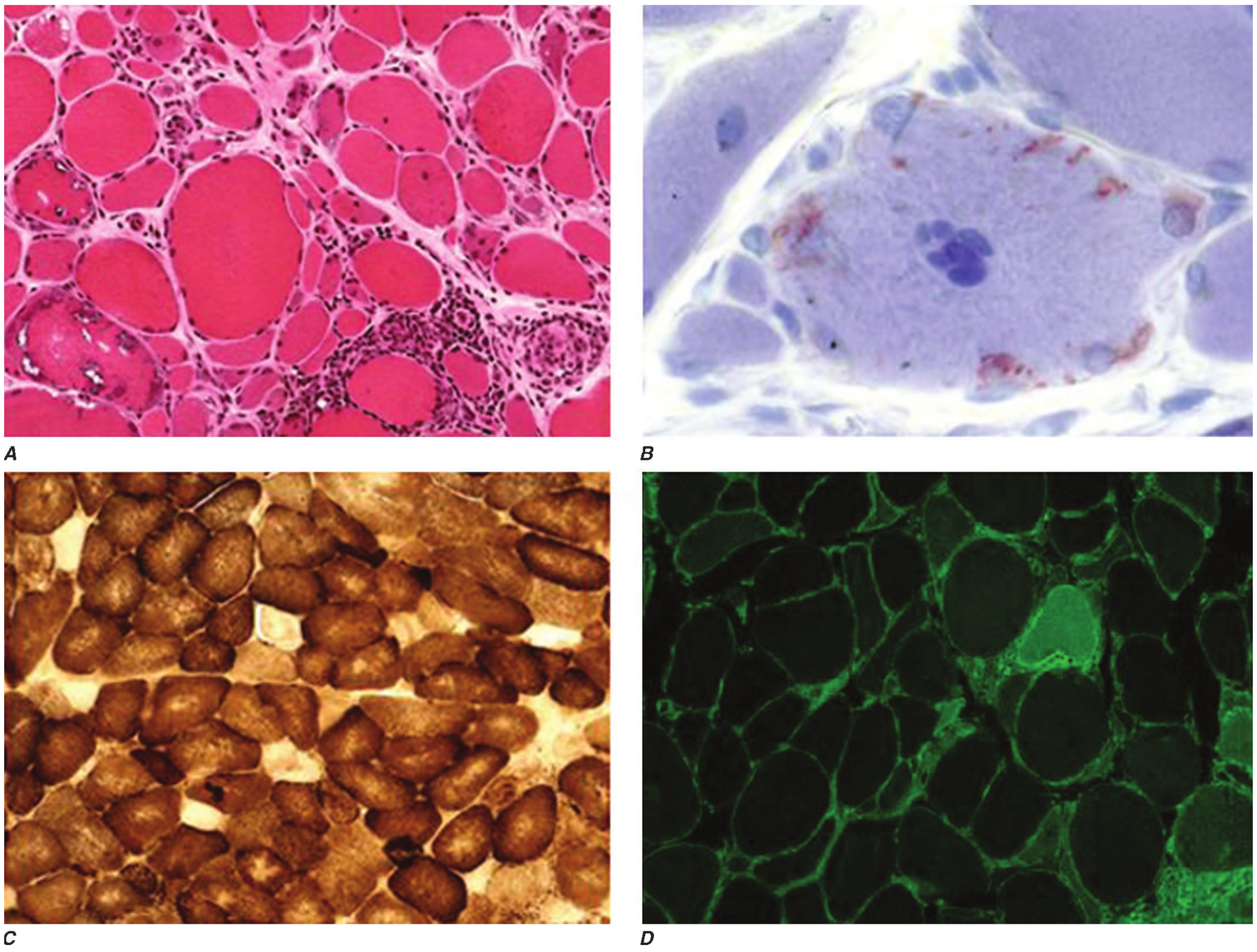


FIGURE 17-5
Cross-sections of a muscle biopsy from a patient with inclusion body myositis demonstrate the typical features of vacuoles with lymphocytic infiltrates surrounding nonvacuolated or necrotic fibers (A), tiny endomysial deposits of amyloid visualized with crystal violet (B), cytochrome oxidase–negative fibers, indicative of mitochondrial dysfunction (C), and ubiquitous major histocompatibility complex class I expression at the periphery of all fibers (D).

In DM the endomysial inflammation is predominantly perivascular or in the interfascicular septae and around—rather than within—the muscle fascicles (Fig. 17-4). T e intramuscular blood vessels show endothelial hyperplasia with tubuloreticular profiles, fibrin thrombi, and obliteration of capillaries. T e muscle fibers undergo necrosis, degeneration, and phagocytosis, often in groups involving a portion of a muscle fasciculus in a wedge-like shape or at the periphery of the fascicle, due to microinfarcts within the muscle. T is results in perifascicular atrophy, characterized by 2–10 layers of atrophic fibers at the periphery of the fascicles. T e presence of perifascicular atrophy is diagnostic of DM, even in the absence *of* in*fl*ammation.

In IBM (Fig. 17-5), there is endomysial inflammation with T cells invading MHC-I-expressing nonvacuolated muscle fibers; basophilic granular deposits distributed around the edge of slit-like vacuoles (rimmed vacuoles); loss of fibers, replaced by fat and connective tissue, hypertrophic fibers, and angulated or round fibers; rare eosinophilic cytoplasmic inclusions; abnormal mitochondria characterized by the presence of ragged-red fibers or cytochrome oxidase–negative fibers; and amyloid deposits within or next to the vacuoles best visualized with crystal violet or Congo-red staining viewed with fluorescent optics. Electron microscopy demonstrates filamentous inclusions in the vicinity of the rimmed vacuoles. In at least 15% of patients with the typical clinical phenotype of IBM, there is brisk inflammation in the muscle biopsy but no vacuoles or amyloid deposits, leading to an erroneous diagnosis of PM. Such patients are often referred to as having "clinical IBM." Close clinicopathologic correlations are therefore essential; if uncertain, a repeat muscle biopsy from another site is often helpful.

TREATMENT Therapy of Inf ammatory Myopathies

T e goal of therapy is to improve muscle strength, thereby improving function in activities of daily living, and ameliorate the extramuscular manifestations (rash, dysphagia, dyspnea, fever). When strength improves, the serum CK falls concurrently; however, the reverse is not always true. Unfortunately, there is a common tendency to "chase" or treat the CK level instead of the muscle weakness, a practice that has led to prolonged and unnecessary use of immunosuppressive drugs and erroneous assessment of their ef cacy. It is prudent to discontinue these drugs if, after an adequate trial, there is no objective improvement in muscle strength whether or not CK levels are reduced. Agents used in the treatment of PM and DM include the following:

1. Glucocorticoids. Oral prednisone is the initial treatment of choice; the effectiveness and side effects of this therapy determine the future need for stronger immunosuppressive drugs. High-dose prednisone, at least 1 mg/kg per day, is initiated as early in the disease as possible. After 3–4 weeks, prednisone is tapered slowly over a period of 10 weeks to 1 mg/kg every other day. If there is evidence of ef cacy and no serious side effects, the dosage is then further reduced by 5 or 10 mg every 3–4 weeks until the lowest possible dose that controls the disease is reached. T e ef cacy of prednisone is determined by an objective increase in muscle strength and activities of daily living, which almost always occurs by the third month of therapy. A feeling of increased energy or a reduction of the CK level without a concomitant increase in muscle strength is not a reliable sign of improvement. If prednisone provides no objective benefit after ~3 months of high-dose therapy, the disease is probably unresponsive to the drug and tapering should be accelerated while the next-in-line immunosuppressive drug is started. Although controlled trials have not been performed, almost all patients with true PM or DM respond to glucocorticoids to some degree and *f*or some period o*f* time; in general, DM responds better than PM.

   T e long-term use of prednisone may cause increased weakness associated with a normal or unchanged CK level; this effect is referred to as steroid myopathy. In a patient who previously responded to high doses of prednisone, the development of new weakness may be related to steroid myopathy or to disease activity that either will respond to a higher dose of glucocorticoids or has become glucocorticoid-resistant. In uncertain cases, the prednisone dosage can be steadily increased or decreased as desired: the cause of the weakness is usually evident in 2–8 weeks.
2. Other immunosuppressive drugs. Approximately 75% of patients ultimately require additional treatment. T is occurs when a patient fails to respond adequately to glucocorticoids after a 3-month trial, the patient becomes glucocorticoid-resistant, glucocorticoid-related side effects appear, attempts to lower the prednisone dose repeatedly result in a new relapse, or rapidly progressive disease with evolving severe weakness and respiratory failure develops.

   T e following drugs are commonly used but have never been tested in controlled studies: (1) Azathioprine is well tolerated, has few side effects, and appears to be as effective for long-term therapy as other drugs. T e dose is up to 3 mg/kg daily. (2) Methotrexate has a faster onset of action than azathioprine. It is given orally starting at 7.5 mg weekly for the first 3 weeks, with gradual dose escalation by 2.5 mg per week to a total of 25 mg weekly. A rare side effect is methotrexate pneumonitis, which can be dif cult to distinguish from the interstitial lung disease of the primary myopathy associated with Jo-1 antibodies (described above). (3) Mycophenolate mo*f*etil also has a faster onset of action than azathioprine. At doses up to 2.5 or 3 g/d in two divided doses, it is well tolerated for long-term use. (4) Monoclonal anti-CD20 antibody (rituximab) has been shown in a small uncontrolled series to benefit

patients with DM and PM, but a controlled study did not show differences between patients randomized 8 weeks apart. (5) Cyclosporine has inconsistent and mild benefit. (6) Cyclophosphamide (0.5–1 g/m^2 IV monthly for 6 months) has limited success and significant toxicity. (7) Tacrolimus (formerly known as Fk506) has been effective in some dif cult cases of PM especially with interstitial lung disease.

3. Immunomodulation. In a controlled trial of patients with refractory DM, IVIg improved not only strength and rash but also the underlying immunopathology. T e benefit is often short-lived (≤8 weeks), and repeated infusions every 6–8 weeks are generally required to maintain improvement. A dose of 2 g/kg divided over 2–5 days per course is recommended. Uncontrolled observations suggest that IVIg may also be beneficial for patients with PM. Neither plasmapheresis nor leukapheresis appears to be effective in PM and DM.

T e following sequential empirical approach to the treatment of PM and DM is suggested: Step 1: high-dose prednisone; Step 2: azathioprine, mycophenolate, or methotrexate for steroid-sparing effect; Step 3: IVIg; Step 4: a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug, and general health: rituximab, cyclosporine, cyclophosphamide, or tacrolimus. Patients with interstitial lung disease may benefit from aggressive treatment with cyclophosphamide or tacrolimus.

A patient with presumed PM who has not responded to any form of immunotherapy most likely has IBM or another disease, usually a metabolic myopathy, a muscular dystrophy, a drug-induced myopathy, or an endocrinopathy. In these cases, a repeat muscle biopsy and a renewed search for another cause of the myopathy is indicated.

Calcinosis, a manifestation of DM, is dif cult to treat; however, new calcium deposits may be prevented if the primary disease responds to the available therapies. Bisphosphonates, aluminum hydroxide, probenecid, colchicine, low doses of warfarin, calcium blockers, and surgical excision have all been tried without success.

IBM is generally resistant to immunosuppressive therapies. Prednisone together with azathioprine or methotrexate is often tried for a few months in newly diagnosed patients, although results are generally disappointing. Because occasional patients may feel subjectively weaker after these drugs are discontinued, some clinicians prefer to maintain these patients on low-dose, every-other-day prednisone along with mycophenolate in an effort to slow disease progression, even though there is no objective evidence or controlled study to support this practice. In two controlled studies of IVIg in IBM, minimal benefit in up to 30% of patients was found; the strength gains, however, were not of suf cient magnitude to justify its routine use. Another trial of IVIg combined with prednisone was ineffective. Nonetheless, some experts believe that a 2- to 3-month trial with IVIg may be reasonable for selected patients with IBM who experience rapid progression of muscle weakness or choking episodes due to worsening dysphagia.

PROGNOSIS

T e 5-year survival rate for treated patients with PM and DM is ~95%, and the 10-year survival rate is 84%; death is usually due to pulmonary, cardiac, or other systemic complications. T e prognosis is worse for patients who are severely affected at presentation, when initial treatment is delayed, and in cases with severe dysphagia or respiratory dif culties. Older patients and those with associated cancer also have a worse prognosis. DM responds more favorably to therapy than PM and thus has a better prognosis. Most patients improve with therapy, and many make a full functional recovery, which is often sustained with maintenance therapy. Up to 30% may be left with some residual muscle weakness. Relapses may occur at any time.

IBM has the least favorable prognosis of the inflammatory myopathies. Most patients will require the use of an assistive device such as a cane, walker, or wheelchair within 5–10 years of onset. In general, the older the age of onset in IBM, the more rapidly progressive is the course.

CHAPTER 18

APPROACH TO ARTICULAR AND MUSCULOSKELETAL DISORDERS

John J. Cush

Musculoskeletal complaints account for >315 million outpatient visits per year and over 20% of all outpatient visits in the United States. T e Centers for Disease Control and Prevention estimate that 22.7% (52.5 million) of the U.S. population has physician-diagnosed arthritis and 22 million have significant functional limitation. While many patients will have self-limited conditions requiring minimal evaluation and only symptomatic therapy and reassurance, specific musculoskeletal presentations or their persistence may herald a more serious condition that requires further evaluation or laboratory testing to establish a diagnosis. T e goal of the musculoskeletal evaluation is to formulate a differential diagnosis that leads to an accurate diagnosis and timely therapy, while avoiding excessive diagnostic testing and unnecessary treatment **(Table 18-1)**. T ere are several urgent conditions that must be diagnosed promptly to avoid significant morbid or mortal sequelae. T ese "red flag" diagnoses include septic arthritis, acute crystal-induced arthritis (e.g., gout), and fracture. Each may be suspected by its acute onset and monarticular or focal musculoskeletal pain (see below).

Despite well-known links between certain disorders and laboratory testing, the majority of individuals with musculoskeletal complaints can be diagnosed with a thorough history and a comprehensive physical and musculoskeletal examination. T e initial encounter should determine whether the musculoskeletal complaint signals a red flag condition (septic arthritis, gout, or fracture) or not. T e evaluation should proceed to ascertain if the complaint is (1) articular or nonarticular in origin, (2) inf ammatory or noninf ammatory in nature, (3) acute or chronic in duration, and (4) localized (monarticular) or widespread (polyarticular) in distribution.

With such an approach and an understanding of the pathophysiologic processes, the musculoskeletal complaint or presentation can be characterized (e.g., acute inflammatory monarthritis or a chronic noninflammatory, nonarticular widespread pain) to narrow the diagnostic possibilities. A diagnosis can be made in the vast majority of individuals. However, some patients will not fit immediately into an established diagnostic category. Many musculoskeletal disorders resemble each other at the outset, and some may take weeks or months (but not years) to evolve into a recognizable diagnostic entity. T is consideration should temper the desire to establish a definitive diagnosis at the first encounter.

TABLE 18-1

EVALUATION OF PATIENTS WITH MUSCULOSKELETAL COMPLAINTS
Goals
Accurate diagnosis
Timely provision of therapy
Avoidance of unnecessary diagnostic testing
Identification of acute, focal/monarticular "red flag" conditions
Approach
Determination of chronology (acute vs chronic)
Determination of the nature of the pathologic process (inflammatory vs noninflammatory)
Determination of the extent of involvement (monarticular, polyarticular, focal, widespread)
Anatomic localization of complaint (articular vs nonarticular)
Consider the most common disorders first
Formulate a dif erential diagnosis

ARTICULAR VERSUS NONARTICULAR

T e musculoskeletal evaluation must discriminate the anatomic origin(s) of the patient's complaint. For

example, ankle pain can result from a variety of pathologic conditions involving disparate anatomic structures, including gonococcal arthritis, calcaneal fracture, Achilles tendinitis, plantar fasciitis, cellulitis, and peripheral or entrapment neuropathy. Distinguishing between articular and nonarticular conditions requires a careful and detailed examination. Articular structures include the synovium, synovial fluid, articular cartilage, intraarticular ligaments, joint capsule, and juxtaarticular bone. Nonarticular (or periarticular) structures, such as supportive extraarticular ligaments, tendons, bursae, muscle, fascia, bone, nerve, and overlying skin, may be involved in the pathologic process. Although musculoskeletal complaints are often ascribed to the joints, nonarticular disorders more frequently underlie such complaints. Distinguishing between these potential sources of pain may be challenging to the unskilled examiner. Articular disorders may be characterized by deep or diffuse pain, pain or limited range of motion on active and passive movement, and swelling (caused by synovial proliferation, effusion, or bony enlargement), crepitation, instability, "locking," or deformity. By contrast, nonarticular disorders tend to be painful on active, but not passive (or assisted), range of motion. Periarticular conditions often demonstrate point or focal tenderness in regions adjacent to articular structures, are elicited with a specific movement or position, and have physical findings remote from the joint capsule. Moreover, nonarticular disorders seldom demonstrate swelling, crepitus, instability, or deformity of the joint itself.

INFLAMMATORY VERSUS NONINFLAMMATORY DISORDERS

In the course of a musculoskeletal evaluation, the examiner should determine the nature of the underlying pathologic process and whether inflammatory or noninflammatory findings exist. Inflammatory disorders may be infectious (Neisseria gonorrhoeae or Mycobacterium tuberculosis), crystal-induced (gout, pseudogout), immune-related (rheumatoid arthritis [RA], systemic lupus erythematosus [SLE]), reactive (rheumatic fever, reactive arthritis), or idiopathic. Inflammatory disorders may be identified by any of the four cardinal signs of inflammation (erythema, warmth, pain, or swelling), systemic symptoms (fatigue, fever, rash, weight loss), or laboratory evidence of inflammation (elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], thrombocytosis, anemia of chronic disease, or hypoalbuminemia). Articular stiffness commonly accompanies chronic musculoskeletal disorders. T e duration of stiffness may be prolonged (hours) with inflammatory disorders (such as RA or polymyalgia rheumatica) and may improve with activity. By contrast, intermittent stiffness (also known as gel phenomenon) is typical of noninflammatory conditions (such as osteoarthritis [OA]), shorter in duration (<60 min), and exacerbated by activity. Fatigue may accompany inflammation (as seen in RA and polymyalgia rheumatica) but may also be a consequence of fibromyalgia (a noninflammatory disorder), chronic pain, poor sleep, depression, anemia, cardiac failure, endocrinopathy, or malnutrition. Noninflammatory disorders may be related to trauma (rotator cuff tear), repetitive use (bursitis, tendinitis), degeneration or ineffective repair (OA), neoplasm (pigmented villonodular synovitis), or pain amplification (fibromyalgia). Noninflammatory disorders are often characterized by pain without synovial swelling or warmth, absence of inflammatory or systemic features, daytime gel phenomena rather than morning stiffness, and normal (for age) or negative laboratory investigations.

Identification of the nature of the underlying process and the site of the complaint will enable the examiner to characterize the musculoskeletal presentation (e.g., acute inflammatory monarthritis, chronic noninflammatory, nonarticular widespread pain), narrow the diagnostic considerations, and assess the need for immediate diagnostic or therapeutic intervention or for continued observation. **Figure 18-1** presents an algorithmic approach to the evaluation of patients with musculoskeletal complaints. T is approach relies on clinical and historic features, rather than laboratory testing, to diagnose many common rheumatic disorders.

A simpler, alternative approach would consider the most commonly encountered complaints first, based on frequency in younger versus older populations. T e most prevalent causes of musculoskeletal complaints are shown in **Fig. 18-2**. Because trauma, fracture, overuse syndromes, and fibromyalgia are among the most common causes of joint pain, these should be considered during the initial encounter. If these possibilities are excluded, other frequently occurring disorders should be considered according to the patient's age. Hence, those younger than 60 years are commonly affected by repetitive use/strain disorders, gout (men only), RA, spondyloarthritis, and uncommonly, infectious arthritis. Patients over age 60 years are frequently affected by OA, crystal (gout and pseudogout) arthritis, polymyalgia rheumatica, osteoporotic fracture, and uncommonly, septic arthritis. T ese conditions are between 10 and 100 times more prevalent than other serious autoimmune conditions, such as SLE, systemic sclerosis (scleroderma), polymyositis, and vasculitis.

CLINICAL HISTORY

Additional historic features may reveal important clues to the diagnosis. Aspects of the patient profile,

ALGORITHM FOR MUSCULOSKELETAL COMPLAINTS

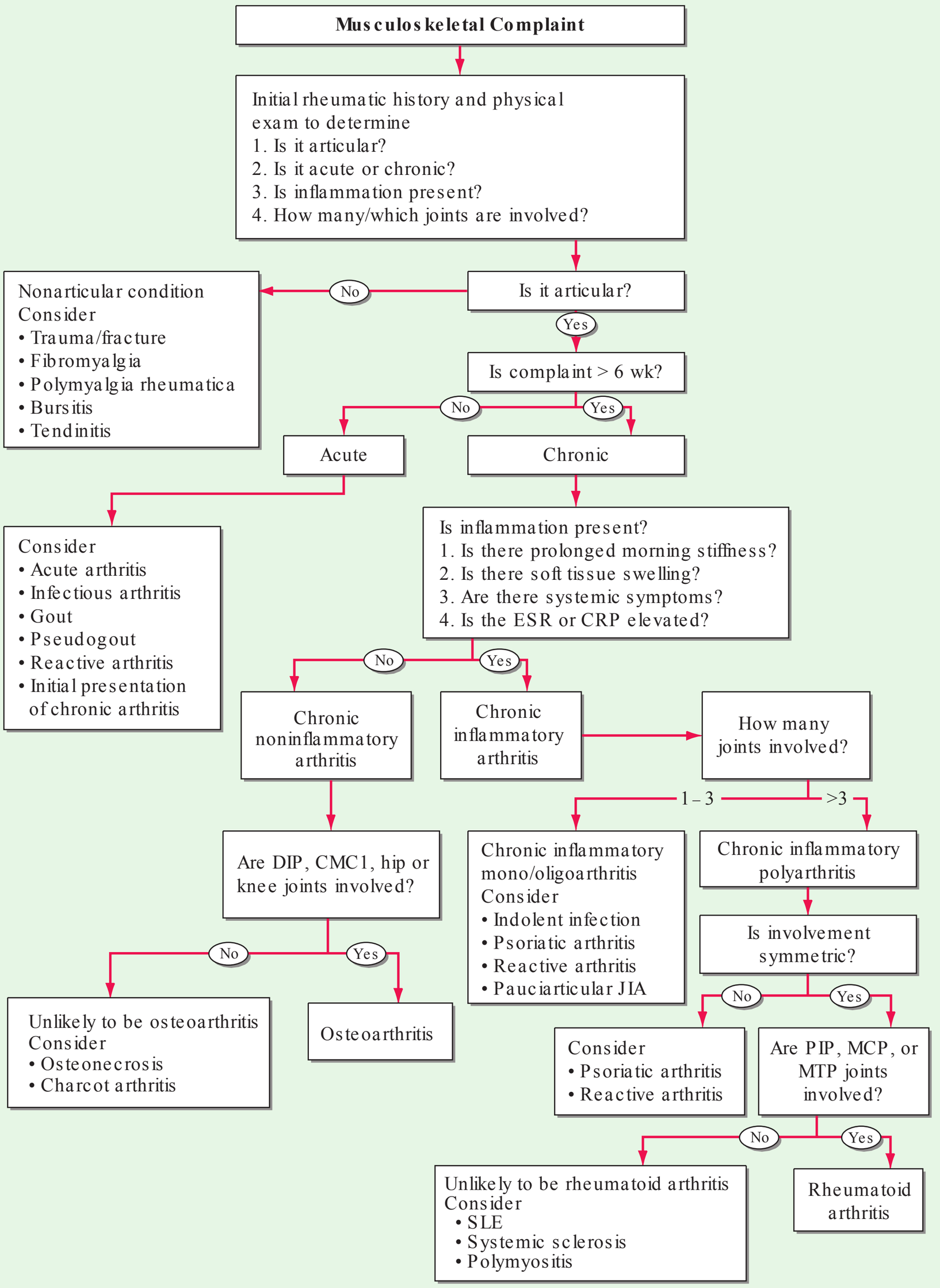


FIGURE 18-1

Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus.

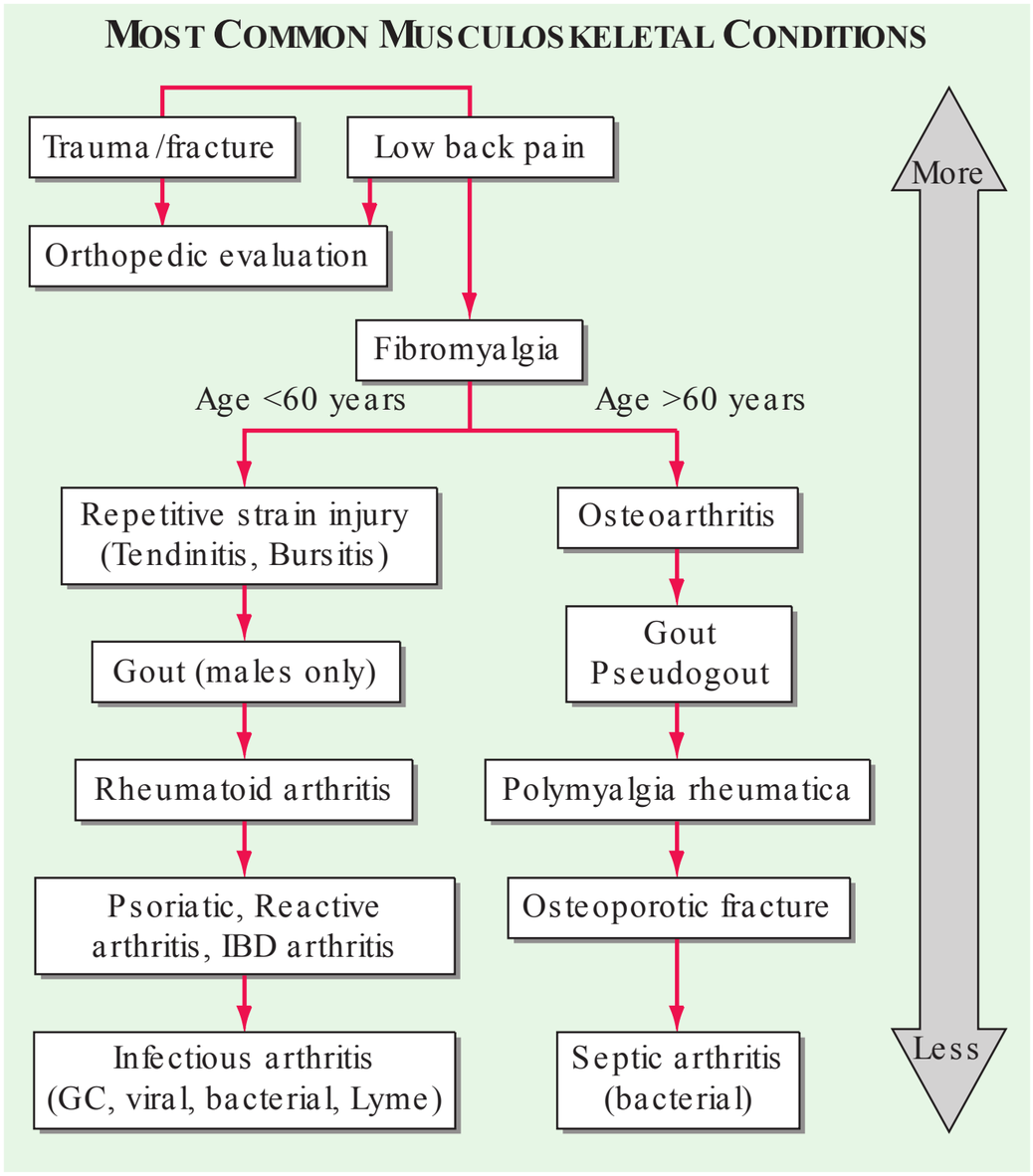


FIGURE 18-2
Algorithm for consideration of the most common musculoskeletal conditions. GC, gonococcal; IBD, inflammatory bowel disease.

complaint chronology, extent of joint involvement, and precipitating factors can provide important information. Certain diagnoses are more frequent in different age groups. SLE and reactive arthritis occur more frequently in the young, whereas fibromyalgia and RA are frequent in middle age, and OA and polymyalgia rheumatica are more prevalent among the elderly. Diagnostic clustering is also evident when sex and race are considered. Gout, spondyloarthritis, and ankylosing spondylitis are more common in men, whereas RA, fibromyalgia, and lupus are more frequent in women. Racial predilections may be evident. Thus, polymyalgia rheumatica, giant cell arteritis, and granulomatosis with polyangiitis (GPA; formerly called Wegener's granulomatosis) commonly affect whites, whereas sarcoidosis and SLE more commonly affect African Americans. Familial aggregation is most common with ankylosing spondylitis, gout, and Heberden's nodes of OA.

The chronology of the complaint is an important diagnostic feature and can be divided into the onset, evolution, and duration. The onset of disorders such as septic arthritis or gout tends to be abrupt, whereas OA, RA, and fibromyalgia may have more indolent presentations. The patients' complaints may evolve differently and be classified as chronic (OA), intermittent (crystal or Lyme arthritis), migratory (rheumatic fever, gonococcal or viral arthritis), or additive (RA, psoriatic arthritis). Musculoskeletal disorders are typically classified as acute or chronic based on a symptom duration that is either less than or greater than 6 weeks, respectively. Acute arthropathies tend to be infectious, crystal-induced, or reactive. Chronic conditions include noninflammatory or immunologic arthritides (e.g., OA, RA) and nonarticular disorders (e.g., fibromyalgia).

The extent or distribution of articular involvement is often informative. Articular disorders are classified based on the number of joints involved, as either monarticular (one joint), oligoarticular or pauciarticular (two or three joints), or polyarticular (four or more joints). Although crystal and infectious arthritis are often mono- or oligoarticular, OA and RA are polyarticular disorders. Nonarticular disorders may be classified as either focal or widespread. Complaints secondary to tendinitis or carpal tunnel syndrome are typically focal, whereas weakness and myalgia, caused by polymyositis or fibromyalgia, are more widespread in their presentation. Joint involvement in RA tends to be symmetric and polyarticular. By contrast, spondyloarthritis, reactive arthritis, gout, and sarcoid are often asymmetric and oligoarticular. OA and psoriatic arthritis may be either symmetric or asymmetric and oligo- or polyarticular. The upper extremities are frequently involved in RA and OA, whereas lower extremity arthritis is characteristic of reactive arthritis and gout at their onset. Involvement of the axial skeleton is common in OA and ankylosing spondylitis but is infrequent in RA, with the notable exception of the cervical spine.

The clinical history should also identify precipitating events, such as trauma (osteonecrosis, meniscal tear), drug administration **(Table 18-2)**, antecedent or intercurrent infection (rheumatic fever, reactive arthritis, hepatitis), or illnesses that may have contributed to the patient's complaint. Certain comorbidities may have musculoskeletal consequences. This is especially so for diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), depression or insomnia (fibromyalgia), myeloma (low back pain), cancer (myositis), and osteoporosis (fracture) or when using certain drugs such as glucocorticoids (osteonecrosis, septic arthritis) and diuretics or chemotherapy (gout) (Table 18-2).

Lastly, a thorough rheumatic review *of* systems may disclose useful diagnostic information. A variety of musculoskeletal disorders may be associated with systemic features such as fever (SLE, infection), rash (SLE, psoriatic arthritis), nail abnormalities (psoriatic or reactive arthritis), myalgias (fibromyalgia, statin- or drug-induced myopathy), or weakness (polymyositis, neuropathy). In addition, some conditions are associated with involvement of other organ systems including the eyes (Behçet's disease, sarcoidosis, spondyloarthritis), gastrointestinal tract (systemic sclerosis, inflammatory bowel disease), genitourinary tract (reactive arthritis, gonococcemia), or nervous system (Lyme disease, vasculitis).

TABLE 18-2

DRUG-INDUCED MUSCULOSKELETAL CONDITIONS

Arthralgias
Quinidine, cimetidine, beta blockers, quinolones, chronic acyclovir, interferons, IL-2, nicardipine, vaccines, rifabutin, aromatase and HIV protease inhibitors

Myalgias/myopathy
Glucocorticoids, penicillamine, hydroxychloroquine, AZT, lovastatin, simvastatin, atorvastatin, pravastatin, clofibrate, amiodarone, interferon, IL-2, alcohol, cocaine, paclitaxel, docetaxel, imatinib mesylate, colchicine, quinolones, cyclosporine, tacrolimus, protease inhibitors

Tendon rupture/tendinitis
Quinolones, glucocorticoids, isotretinoin, statins, collagenase injections

Gout
Diuretics, aspirin, cytotoxics, cyclosporine, alcohol, moonshine, ethambutol, fructose-containing soft drinks

Drug-induced lupus
Hydralazine, procainamide, quinidine, phenytoin, carbamazepine, methyldopa, isoniazid, chlorpromazine, lithium, penicillamine, tetracyclines, TNF inhibitors, ACE inhibitors, ticlopidine

Drug-induced subacute lupus
Proton pump inhibitors, calcium channel blockers (diltiazem), ACE inhibitors, TNF inhibitors, terbinafine, interferons (α and β-1a), paclitaxel, docetaxel, HCTZ

Osteonecrosis
Glucocorticoids, alcohol, radiation, bisphosphonates

Osteopenia
Glucocorticoids, chronic heparin, phenytoin

Systemic sclerosis (scleroderma)
Vinyl chloride, bleomycin, baricitinib, pentazocine, organic solvents, carbidopa, tryptophan, rapeseed oil

Vasculitis
Allopurinol, amphetamines, cocaine (often levamisole adulterated), thiazides, penicillamine, propylthiouracil, montelukast, TNF inhibitors, hepatitis B vaccine, trimethoprim/sulfamethoxazole, minocycline, hydralazine

Abbreviations: ACE, angiotensin-converting enzyme; AZT, zidovudine; HCTZ, hydrochlorothiazide; IL-2, interleukin 2; TNF, tumor necrosis factor.

RHEUMATOLOGIC EVALUATION OF THE ELDERLY

The incidence of rheumatic diseases rises with age, such that 58% of those >65 years will have joint complaints. Musculoskeletal disorders in elderly patients are often not diagnosed because the signs and symptoms may be insidious, overlooked, or overshadowed by comorbidities. These difficulties are compounded by the diminished reliability of laboratory testing in the elderly, who often manifest nonpathologic abnormal results. For example, the ESR may be misleadingly elevated, and low-titer positive tests for rheumatoid factor and antinuclear antibodies (ANAs) may be seen in up to 15% of elderly patients. Although nearly all rheumatic disorders afflict the elderly, geriatric patients are particularly prone to OA, osteoporosis, osteoporotic fractures, gout, pseudogout, polymyalgia rheumatica, vasculitis, and drug-induced disorders (Table 18-2). The elderly should be approached in the same manner as other patients with musculoskeletal complaints, but with an emphasis on identifying the potential rheumatic consequences of medical comorbidities and therapies. The physical examination should identify the nature of the musculoskeletal complaint as well as coexisting diseases that may influence diagnosis and choice of treatment.

RHEUMATOLOGIC EVALUATION OF THE HOSPITALIZED PATIENT

Evaluation of a hospitalized patient with rheumatic complaints differs from that of an outpatient, owing to greater symptom severity, more acute presentations, and greater interplay of comorbidities. Patients with rheumatic disorders tend to be admitted for one of several reasons: (1) acute onset of inflammatory arthritis; (2) undiagnosed systemic or febrile illness; (3) musculoskeletal trauma; (4) exacerbation or deterioration of an existing autoimmune disorder (e.g., SLE); or (5) new medical comorbidities (e.g., thrombotic event, lymphoma, infection) arising in patients with an established rheumatic disorder. Notably, rheumatic patients are seldom if ever admitted because of widespread pain or serologic abnormalities or for the initiation of new therapies.

Acute monarticular inflammatory arthritis may be a "red flag" condition (e.g., septic arthritis, gout, pseudogout) that will require arthrocentesis and, on occasion, hospitalization if infection is suspected. However, new-onset inflammatory polyarthritis will have a wider differential diagnosis (e.g., RA, hepatitis-related arthritis, serum sickness, drug-induced lupus, polyarticular septic arthritis) and may require targeted laboratory investigations rather than synovial fluid analyses. Patients with febrile, multisystem disorders will require exclusion of crystal, infectious, or neoplastic etiologies and an evaluation driven by the dominant symptom/finding with the greatest specificity. Conditions worthy of consideration may include gout or pseudogout, vasculitis (giant cell arteritis in the elderly or polyarteritis nodosa in younger patients), adult-onset Still's disease, SLE, antiphospholipid syndrome, and sarcoidosis. Because the misdiagnosis of connective tissue disorders is common, patients who present with a reported preexisting rheumatic condition (e.g., SLE, RA, ankylosing spondylitis) should have their diagnosis confirmed by careful

history, physical and musculoskeletal examination, and review of their medical records. It is important to note that when established rheumatic disease patients are admitted to the hospital, it is usually not for a medical problem related to their autoimmune disease, but rather because of either a comorbid condition or complication of drug therapy. Patients with chronic inflammatory disorders (e.g., RA, SLE, psoriasis) have an augmented risk of infection, cardiovascular events, and neoplasia.

Certain conditions, such as acute gout, can be precipitated in hospitalized patients by surgery, dehydration, or other events and should be considered when hospitalized patients are evaluated for the acute onset of a musculoskeletal condition. Lastly, overly aggressive and unfocused laboratory testing will often yield abnormal findings that are better explained by the patient's preexisting condition(s) rather than a new inflammatory or autoimmune disorder.

PHYSICAL EXAMINATION

The goal of the physical examination is to ascertain the structures involved, the nature of the underlying pathology, the functional consequences of the process, and the presence of systemic or extraarticular manifestations. A knowledge of topographic anatomy is necessary to identify the primary site(s) of involvement and differentiate articular from nonarticular disorders. The musculoskeletal examination depends largely on careful inspection, palpation, and a variety of specific physical maneuvers to elicit diagnostic signs **(Table 18-3)**. Although most articulations of the appendicular skeleton can be examined in this manner, adequate inspection and palpation are not possible for many axial (e.g., zygapophyseal) and inaccessible (e.g., sacroiliac or hip) joints. For such joints, there is a greater reliance on specific maneuvers and imaging for assessment.

Examination of involved and uninvolved joints will determine whether pain, warmth, erythema, or swelling is present. The locale and level of pain elicited by palpation or movement should be quantified. One standard would be to count the number of tender joints on palpation of 28 easily examined joints (proximal interphalangeals, metacarpophalangeals, wrists, elbows, shoulders, and knees). Similarly, the number of swollen joints (0–28) can be counted and recorded. Careful examination should distinguish between true articular swelling (caused by bony hypertrophy, synovial effusion or proliferation) and nonarticular (or periarticular) involvement, which usually extends beyond the normal joint margins. Synovial effusion can be distinguished from synovial hypertrophy or bony hypertrophy by palpation or specific maneuvers. For example, small to moderate knee effusions may be identified by the "bulge sign" or "ballottement of the patellae." Bursal effusions (e.g., effusions of the olecranon or prepatellar bursa) are often focal, periarticular, overlie bony prominences, and are fluctuant with sharply defined borders. Joint stability can be assessed by stabilizing the proximal joint, by palpation, and by the application of manual stress to the distal appendage. Subluxation or dislocation, which may be secondary to traumatic, mechanical, or inflammatory causes, can be assessed by inspection and palpation. Joint swelling or volume can be assessed by palpation. Distention of the articular capsule usually causes pain and evident enlargement or fluctuance. The patient will attempt to minimize the pain by maintaining the joint in the position of least intraarticular pressure and greatest volume, usually partial flexion. For this reason, inflammatory effusions may give rise to flexion contractures. Clinically, this may be detected as fluctuant or "squishy" swelling in larger joints and grape-like compressibility in smaller joints. Inflammation may result in fixed flexion deformities or diminished range of motion—especially on extension, when intraarticular pressure is increased. Active and passive range *of* motion should be assessed in all planes, with

TABLE 18-3

GLOSSARY OF MUSCULOSKELETAL TERMS

Crepitus	Apalpable (less commonly audible) vibratory or crackling sensation elicited with joint motion; fine joint crepitus is common and often insignificant in large joints; coarse joint crepitus indicates advanced cartilaginous and degenerative changes (as in osteoarthritis)
Subluxation	Alteration of joint alignment such that articulating surfaces incompletely approximate each other
Dislocation	Abnormal displacement of articulating surfaces such that the surfaces are not in contact
Range of motion	For diarthrodial joints, the arc of measurable movement through which the joint moves in a single plane
Contracture	Loss of full movement resulting from a fixed resistance caused either by tonic spasm of muscle (reversible) or by fibrosis of periarticular structures (permanent)
Deformity	Abnormal shape or size resulting from bony hypertrophy, malalignment of articulating structures, or damage to periarticular supportive structures
Enthesitis	Inflammation of the entheses (tendinous or ligamentous insertions on bone)
Epicondylitis	Infection or inflammation involving an epicondyle

contralateral comparison. A goniometer may be used to quantify the arc of movement. Each joint should be passively manipulated through its full range of motion (including, as appropriate, flexion, extension, rotation, abduction, adduction, lateral bending, inversion, eversion, supination, pronation, medial/lateral deviation, and plantar- or dorsiflexion). Extreme range of motion may be seen with hypermobility syndrome, with joint pain and connective tissue laxity, often associated with Ehlers-Danlos or Marfan's syndrome. Limitation of motion is frequently caused by inflammation, effusion, pain, deformity, contracture, or restriction from neuromyopathic causes. If passive motion exceeds active motion, a periarticular process (e.g., tendinitis, tendon rupture, or myopathy) should be considered. Contractures may reflect antecedent synovial inflammation or trauma. Minor joint crepitus is common during joint palpation and maneuvers but only indicates significant cartilage degeneration as it becomes coarser (e.g., OA). Joint deformity usually indicates a long-standing or aggressive pathologic process. Deformities may result from ligamentous destruction, soft tissue contracture, bony enlargement, ankylosis, erosive disease, subluxation, trauma, or loss of proprioception. Examination of the musculature will document strength, atrophy, pain, or spasm. Appendicular muscle weakness should be characterized as proximal or distal. Muscle strength should be assessed by observing the patient's performance (e.g., walking, rising from a chair, grasping, writing). Strength may also be graded on a 5-point scale: 0 for no movement; 1 for trace movement or twitch; 2 for movement with gravity eliminated; 3 for movement against gravity only; 4 for movement against gravity and resistance; and 5 for normal strength. The examiner should assess for often-overlooked nonarticular or periarticular involvement, especially when articular complaints are not supported by objective findings referable to the joint capsule. The identification of soft tissue/nonarticular pain will prevent unwarranted and often expensive additional evaluations. Specific maneuvers may reveal common nonarticular abnormalities, such as a carpal tunnel syndrome (which can be identified by Tinel's or Phalen's sign). Other examples of soft tissue abnormalities include olecranon bursitis, epicondylitis (e.g., tennis elbow), enthesitis (e.g., Achilles tendinitis), and tender trigger points associated with fibromyalgia.

APPROACH TO REGIONAL RHEUMATIC COMPLAINTS

Although all patients should be evaluated in a logical and thorough manner, many cases with focal musculoskeletal complaints are caused by commonly encountered disorders that exhibit a predictable pattern of onset, evolution, and localization; they can often be diagnosed immediately on the basis of limited historic information and selected maneuvers or tests. Although nearly every joint could be approached in this manner, the evaluation of four common involved anatomic regions—the hand, shoulder, hip, and knee—are reviewed here.

HAND PAIN

Focal or unilateral hand pain may result from trauma, overuse, infection, or a reactive or crystal-induced arthritis. By contrast, bilateral hand complaints commonly suggest a degenerative (e.g., OA), systemic, or inflammatory/immune (e.g., RA) etiology. The distribution or pattern of joint involvement is highly suggestive of certain disorders **(Fig. 18-3)**. Thus, OA (or degenerative arthritis) may manifest as distal interphalangeal (DIP) and proximal interphalangeal (PIP) joint pain with bony hypertrophy sufficient to produce Heberden's and Bouchard's nodes, respectively. Pain, with or without bony swelling, involving the base of the thumb (first carpometacarpal joint) is also highly

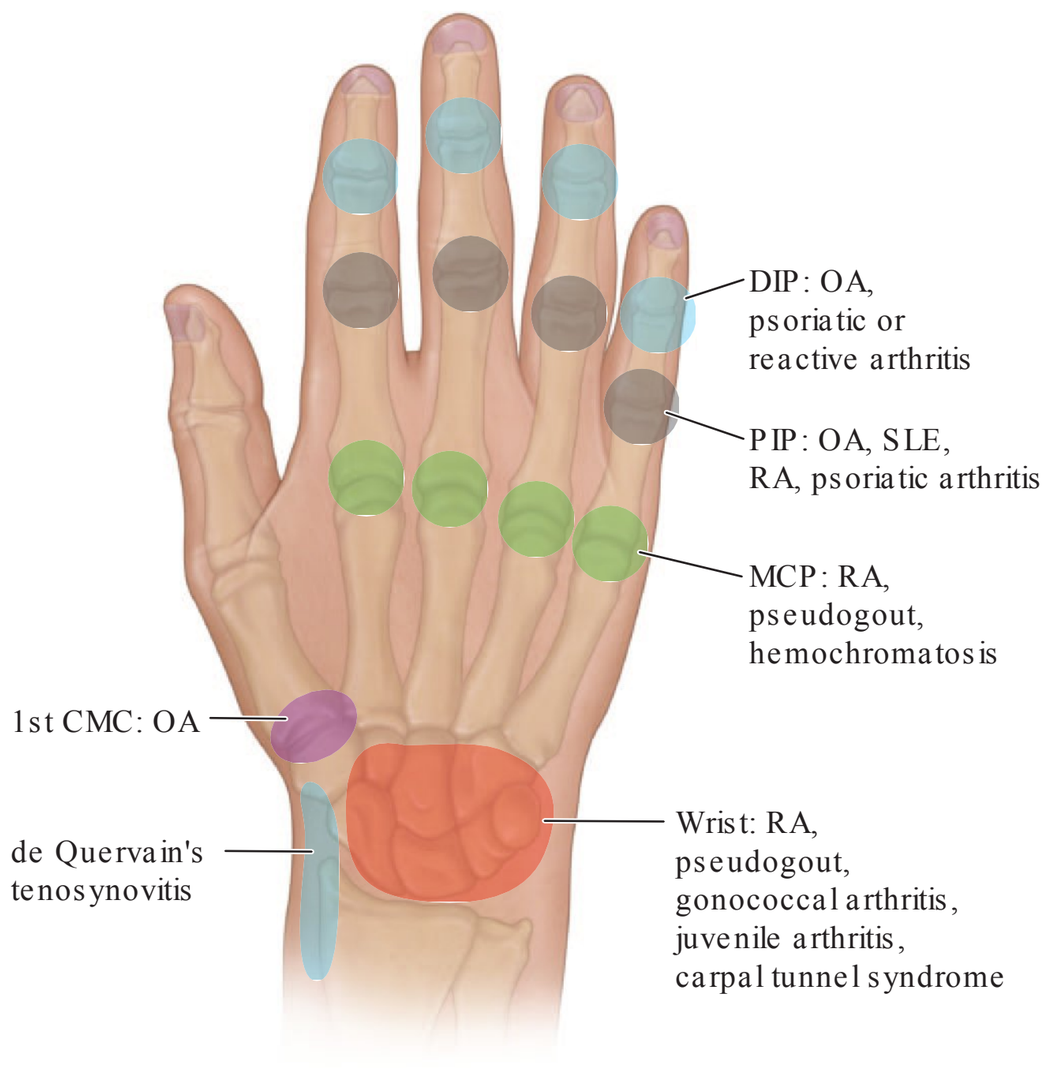


FIGURE 18-3
Sites of hand or wrist involvement and their potential disease associations. CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. (From JJ Cush et al: Evaluation of musculoskeletal complaints, in Rheumatology: Diagnosis and Therapeutics, 2nd ed, JJ Cush et al [eds]. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 3–20. Used with permission from Dr. John J. Cush.)

suggestive of OA. By contrast, RA tends to cause symmetric, polyarticular involvement of the PIP, metacarpophalangeal (MCP), intercarpal, and carpometacarpal joints (wrist) with pain and palpable synovial tissue hypertrophy. Psoriatic arthritis may mimic the pattern of joint involvement seen in OA (DIP and PIP joints), but can be distinguished by the presence of inflammatory signs (erythema, warmth, synovial swelling), with or without carpal involvement, nail pitting, or onycholysis. Whereas lateral or medial subluxations at the PIP or DIP joints are most likely due to inflammatory OA or psoriatic arthritis, dorsal or ventral deformities (swan neck or boutonnière deformities) are typical of RA. Hemochromatosis should be considered when degenerative changes (bony hypertrophy) are seen at the second and third MCP joints with associated radiographic chondrocalcinosis or episodic, inflammatory wrist arthritis.

Dactylitis manifests as soft tissue swelling of the whole digit and may have a sausage-like appearance. Common causes of dactylitis include psoriatic arthritis, spondyloarthritis, juvenile spondylitis, mixed connective tissue disease, systemic sclerosis, sarcoidosis, and sickle cell disease. Soft tissue swelling over the dorsum of the hand and wrist may suggest an inflammatory extensor tendon tenosynovitis possibly caused by gonococcal infection, gout, or inflammatory arthritis (e.g., RA). Tenosynovitis is suggested by localized warmth, swelling, or pitting edema and may be confirmed when the soft tissue swelling tracks with tendon movement, such as flexion and extension of fingers, or when pain is induced while stretching the extensor tendon sheaths (flexing the digits distal to the MCP joints and maintaining the wrist in a fixed, neutral position).

Focal wrist pain localized to the radial aspect may be caused by de Quervain's tenosynovitis resulting from inflammation of the tendon sheath(s) involving the abductor pollicis longus or extensor pollicis brevis (Fig. 18-3). T is commonly results from overuse or follows pregnancy and may be diagnosed with Finkelstein's test. A positive result is present when radial wrist pain is induced after the thumb is flexed and placed inside a clenched fist and the patient actively deviates the hand downward with ulnar deviation at the wrist. Carpal tunnel syndrome is another common disorder of the upper extremity and results from compression of the median nerve within the carpal tunnel. Manifestations include pain in the wrist that may radiate with paresthesia to the thumb, second and third fingers, and radial half of the fourth finger and, at times, atrophy of thenar musculature. Carpal tunnel syndrome is commonly associated with pregnancy, edema, trauma, OA, inflammatory arthritis, and infiltrative disorders (e.g., amyloidosis). T e diagnosis may be suggested by a positive Tinel's or Phalen's sign. With each test, paresthesia in a median nerve distribution is induced or increased by either "thumping" the volar aspect of the wrist (Tinel's sign) or pressing the extensor surfaces of both flexed wrists against each other (Phalen's sign). T e low sensitivity and moderate specificity of these tests may require nerve conduction velocity testing to confirm a suspected diagnosis.

SHOULDER PAIN

During the evaluation of shoulder disorders, the examiner should carefully note any history of trauma, fibromyalgia, infection, inflammatory disease, occupational hazards, or previous cervical disease. In addition, the patient should be questioned as to the activities or movement(s) that elicit shoulder pain. While arthritis is suggested by pain on movement in all planes, pain with specific active motion suggests a periarticular (nonarticular) process. Shoulder pain may originate in the glenohumeral or acromioclavicular joints, subacromial (subdeltoid) bursa, periarticular soft tissues (e.g., fibromyalgia, rotator cuff tear/tendinitis), or cervical spine **(Fig. 18-4)**. Shoulder pain is referred frequently from the cervical spine but may also be referred from

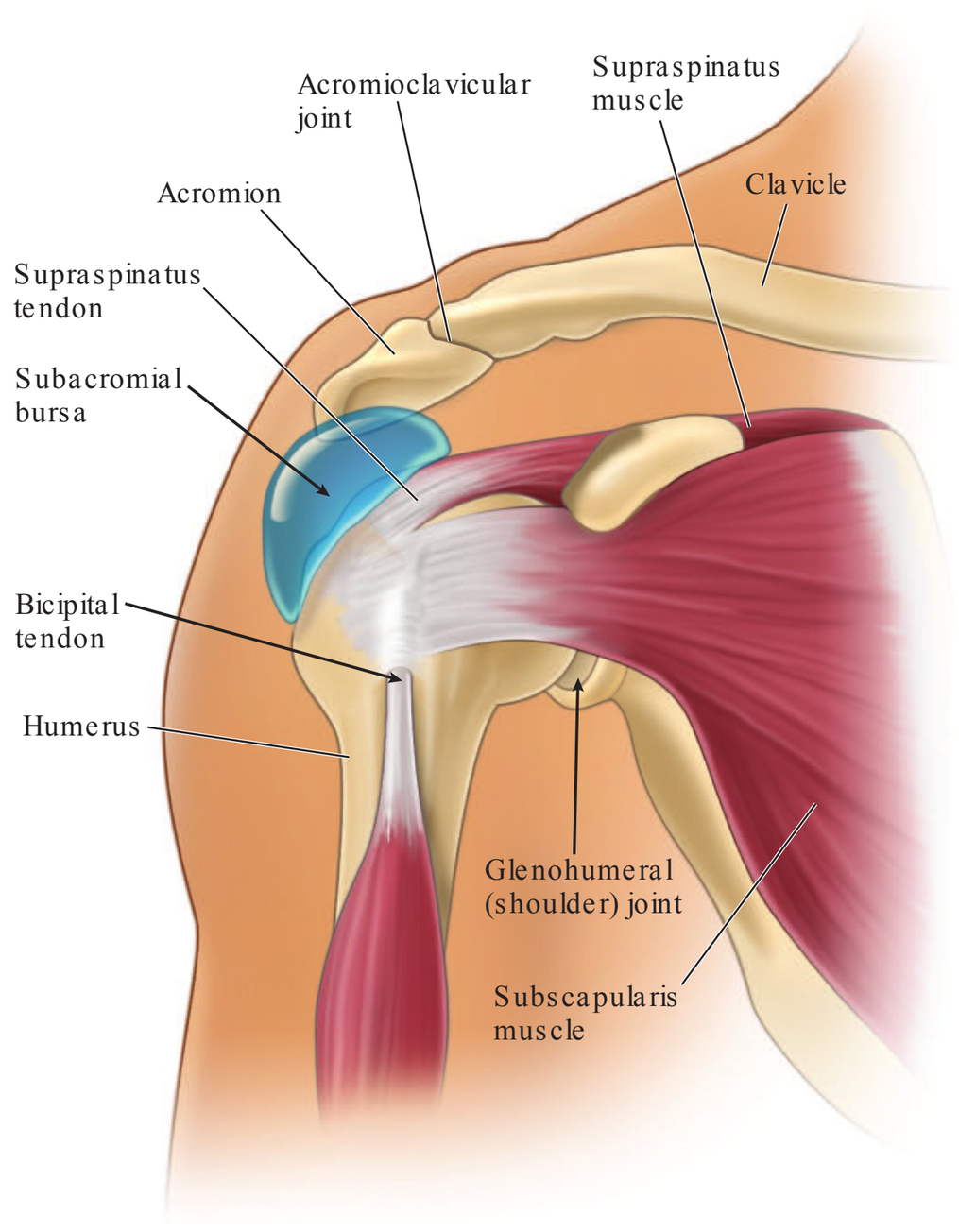


FIGURE 18-4
Origins of shoulder pain. The schematic diagram of the shoulder indicates with arrows the anatomic origins of shoulder pain.

intrathoracic lesions (e.g., a Pancoast tumor) or from gallbladder, hepatic, or diaphragmatic disease. T ese same visceral causes may also manifest as focal scapular pain. Fibromyalgia should be suspected when glenohumeral pain is accompanied by diffuse periarticular (i.e., subacromial, bicipital) pain and tender points (i.e., trapezius or supraspinatus). T e shoulder should be put through its full range of motion both actively and passively (with examiner assistance): forward flexion, extension, abduction, adduction, and internal and external rotation. Manual inspection of the periarticular structures will often provide important diagnostic information. Glenohumeral involvement is best detected by placing the thumb over the glenohumeral joint just medial and inferior to the coracoid process and applying pressure anteriorly while internally and externally rotating the humeral head. Pain localized to this region is indicative of glenohumeral pathology. Synovial effusion or tissue is seldom palpable but, if present, may suggest infection, RA, amyloidosis, or an acute tear of the rotator cuff. T e examiner should apply direct manual pressure over the subacromial bursa that lies lateral to and immediately beneath the acromion (Fig. 18-4). Subacromial bursitis is a frequent cause of shoulder pain. Anterior to the subacromial bursa, the bicipital tendon traverses the bicipital groove. T is tendon is best identified by palpating it in its groove as the patient rotates the humerus internally and externally. Direct pressure over the tendon may reveal pain indicative of bicipital tendinitis. Palpation of the acromioclavicular joint may disclose local pain, bony hypertrophy, or, uncommonly, synovial swelling. Whereas OA and RA commonly affect the acromioclavicular joint, OA seldom involves the glenohumeral joint, unless there is a traumatic or occupational cause.

Rotator cuff tendinitis or tear is a very common cause of shoulder pain. Nearly 30 percent of the elderly will have shoulder pain, with rotator cuff tendinitis or tear as the primary cause. T e rotator cuff is formed by four tendons that attach the scapula to the proximal humerus (supraspinatus, infraspinatus, teres minor, and subscapularis tendons). Of these, the supraspinatus muscle is the most commonly damaged. Rotator cuff tendinitis is suggested by pain on active abduction (but not passive abduction), pain over the lateral deltoid muscle, night pain, and evidence of the impingement signs (pain with overhead arm activities). T e Neer test for impingement is performed by the examiner raising the patient's arm into forced flexion while stabilizing and preventing rotation of the scapula. A positive sign is present if pain develops before 180° of forward flexion. Tear of the rotator cuff is common in the elderly and often results from trauma; it may manifest in the same manner as tendinitis. T e drop arm test is abnormal with supraspinatus pathology and is demonstrated by passive abduction of the arm to 90° by the examiner. If the patient is unable to hold the arm up actively or unable to lower the arm slowly without dropping, the test is positive. Tendinitis or tear of the rotator cuff is best confirmed by magnetic resonance imaging (MRI) or ultrasound.

KNEE PAIN

Knee pain may result from intraarticular (OA, RA) or periarticular (anserine bursitis, collateral ligament strain) processes or be referred from hip pathology. A careful history should delineate the chronology of the knee complaint and whether there are predisposing conditions, trauma, or medications that might underlie the complaint. For example, patellofemoral disease (e.g., OA) may cause anterior knee pain that worsens with climbing stairs. Observation of the patient's gait is also important. T e knee should be carefully inspected in the upright (weight-bearing) and supine positions for swelling, erythema, malalignment, visible trauma, muscle wasting, and leg length discrepancy. T e most common malalignment in the knee is genu varum (bowlegs) or genu valgum (knock-knees) resulting from asymmetric cartilage loss medially or laterally. Bony swelling of the knee joint commonly results from hypertrophic osseous changes seen with disorders such as OA and neuropathic arthropathy. Swelling caused by hypertrophy of the synovium or synovial effusion may manifest as a fluctuant, ballotable, or soft tissue enlargement in the suprapatellar pouch (suprapatellar reflection of the synovial cavity) or regions lateral and medial to the patella. Synovial effusions may also be detected by balloting the patella downward toward the femoral groove or by eliciting a "bulge sign." With the knee extended, the examiner should manually compress, or "milk," synovial fluid down from the suprapatellar pouch and lateral to the patellae. T e application of manual pressure lateral to the patella may cause an observable shift in synovial fluid (bulge) to the medial aspect. T e examiner should note that this maneuver is only effective in detecting small to moderate effusions (<100 mL). Inflammatory disorders such as RA, gout, pseudogout, and psoriatic arthritis may involve the knee joint and produce significant pain, stiffness, swelling, or warmth. A popliteal or Baker's cyst may be palpated with the knee partially flexed and is best viewed posteriorly with the patient standing and knees fully extended to visualize isolated or unilateral popliteal swelling or fullness.

Anserine bursitis is an often missed periarticular cause of knee pain in adults. T e pes anserine bursa underlies the insertion of the conjoined tendons (sartorius, gracilis, semitendinosus) on the anteromedial proximal tibia and may be painful following trauma, overuse, or inflammation. It is often tender in patients

with fibromyalgia, obesity, and knee OA. Other forms of bursitis may also present as knee pain. T e prepatellar bursa is superficial and is located over the inferior portion of the patella. T e infrapatellar bursa is deeper and lies beneath the patellar ligament before its insertion on the tibial tubercle.

Internal derangement of the knee may result from trauma or degenerative processes. Damage to the meniscal cartilage (medial or lateral) frequently presents as chronic or intermittent knee pain. Such an injury should be suspected when there is a history of trauma, athletic activity, or chronic knee arthritis, and when the patient relates symptoms of "locking" or "giving way" of the knee. With the knee flexed 90° and the patient's foot on the table, pain elicited during palpation over the joint line or when the knee is stressed laterally or medially may suggest a meniscal tear. A positive McMurray test may also indicate a meniscal tear. To perform this test, the knee is first flexed at 90°, and the leg is then extended while the lower extremity is simultaneously torqued medially or laterally. A painful click during inward rotation may indicate a lateral meniscus tear, and pain during outward rotation may indicate a tear in the medial meniscus. Lastly, damage to the cruciate ligaments should be suspected with acute onset of pain, possibly with swelling, a history of trauma, or a synovial fluid aspirate that is grossly bloody. Examination of the cruciate ligaments is best accomplished by eliciting a drawer sign. With the patient recumbent, the knee should be partially flexed and the foot stabilized on the examining surface. T e examiner should manually attempt to displace the tibia anteriorly or posteriorly with respect to the femur. If anterior movement is detected, then anterior cruciate ligament damage is likely. Conversely, significant posterior movement may indicate posterior cruciate damage. Contralateral comparison will assist the examiner in detecting significant anterior or posterior movement.

HIP PAIN

T e hip is best evaluated by observing the patient's gait and assessing range of motion. T e vast majority of patients reporting "hip pain" localize their pain unilaterally to the posterior gluteal musculature **(Fig. 18-5)**. Such pain tends to radiate down the posterolateral aspect of the thigh and may or may not be associated with complaints of low back pain. T is presentation frequently results from degenerative arthritis of the lumbosacral spine or disks and commonly follows a dermatomal distribution with involvement of nerve roots between L4 and S1. Sciatica is caused by impingement of the L4, L5, or S1 nerve (i.e., from a herniated disk) and manifests as unilateral neuropathic pain extending from the gluteal region down the posterolateral leg to the foot. Some individuals instead localize their "hip pain" laterally to the area overlying the trochanteric bursa. Because of the depth of this bursa, swelling and warmth are usually absent. Diagnosis of trochanteric bursitis or enthesitis can be confirmed by inducing point tenderness over the trochanteric bursa. Gluteal and trochanteric pain are common findings in fibromyalgia. Range of movement may be limited by pain. Pain in the hip joint is less common and tends to be located anteriorly, over the inguinal ligament; it may radiate medially to the groin. Uncommonly, iliopsoas bursitis may mimic true hip joint pain. Diagnosis of iliopsoas bursitis may be suggested by a history of trauma or inflammatory arthritis. Pain associated with iliopsoas bursitis is localized to the groin or

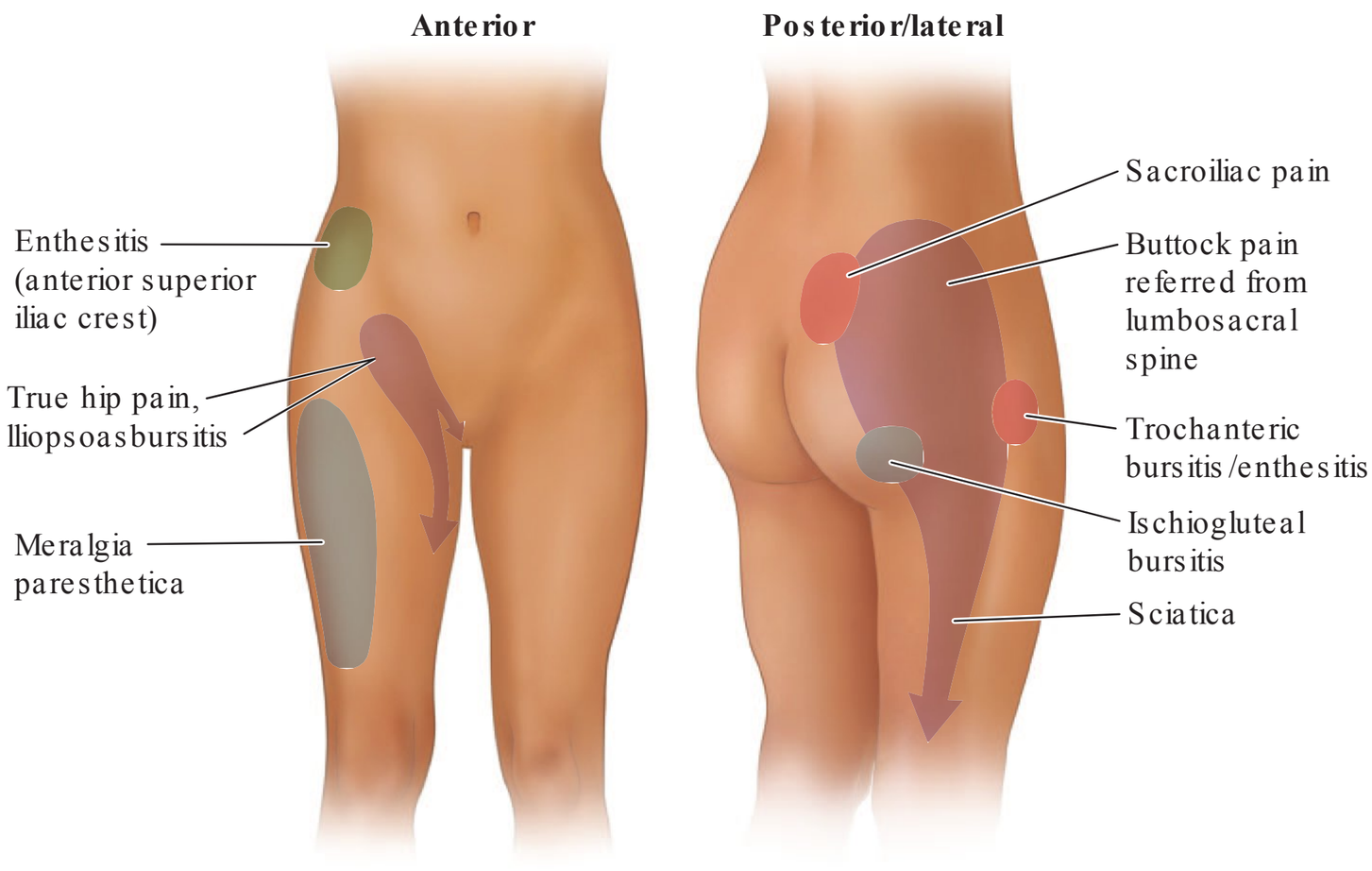


FIGURE 18-5
Origins of hip pain and dysesthesias. (From JJ Cush et al: Evaluation of musculoskeletal complaints, in Rheumatology: Diagnosis and Therapeutics, 2nd ed, JJ Cush et al [eds]. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 3–20. Used with permission from Dr. John J. Cush.)

anterior thigh and tends to worsen with hyperextension of the hip; many patients prefer to flex and externally rotate the hip to reduce the pain from a distended bursa.

LABORATORY INVESTIGATIONS

T e vast majority of musculoskeletal disorders can be easily diagnosed by a complete history and physical examination. An additional objective of the initial encounter is to determine whether additional investigations or immediate therapy is required. Additional evaluation is indicated with: (1) monarticular conditions; (2) traumatic or inflammatory conditions; (3) the presence of neurologic findings; (4) systemic manifestations; or (5) chronic symptoms (>6 weeks) and a lack of response to symptomatic measures. T e extent and nature of the additional investigation should be dictated by the clinical features and suspected pathologic process. Laboratory tests should be used to confirm a specific clinical diagnosis and not be used to screen or evaluate patients with vague rheumatic complaints. Indiscriminate use of broad batteries of diagnostic tests and radiographic procedures is rarely a useful or cost-effective means to establish a diagnosis.

Besides a complete blood count, including a white blood cell (WBC) and differential count, the routine evaluation should include a determination of an acute-phase reactant such as the ESR or CRP, which can be useful in discriminating inflammatory from noninflammatory disorders. Both are inexpensive, easily obtained, and may be elevated with infection, inflammation, autoimmune disorders, neoplasia, pregnancy, renal insufficiency, advanced age, or hyperlipidemia. Extreme elevation of the acute-phase reactants (CRP, ESR) is seldom seen without evidence of serious illness (e.g., sepsis, pleuropericarditis, polymyalgia rheumatica, giant cell arteritis, adult Still's disease).

Serum uric acid determinations are useful in the diagnosis of gout and in monitoring the response to urate-lowering therapy. Uric acid, the end product of purine metabolism, is primarily excreted in the urine. Serum values range from 238 to 516 μmol/L (4.0–8.6 mg/dL) in men; the lower values (178–351 μmol/L [3.0–5.9 mg/dL]) seen in women are caused by the uricosuric effects of estrogen. Urinary uric acid levels are normally <750 mg per 24 h. Although hyperuricemia (especially levels >535 μmol/L [9 mg/dL]) is associated with an increased incidence of gout and nephrolithiasis, levels may not correlate with the severity of articular disease. Uric acid levels (and the risk of gout) may be increased by inborn errors of metabolism (Lesch-Nyhan syndrome), disease states (renal insufficiency, myeloproliferative disease, psoriasis), or drugs (alcohol, cytotoxic therapy, thiazides). Although nearly all patients with gout will demonstrate hyperuricemia at some time during their illness, up to 50% of patients with an acute gouty attack will have normal serum uric acid levels. Monitoring serum uric acid may be useful in assessing the response to urate-lowering therapy or chemotherapy, with the target goal being a serum urate <6 mg/dL.

Serologic tests for rheumatoid factor (RF), cyclic anticitrullinated peptide (CCP or ACPA) antibodies, ANAs, complement levels, Lyme and antineutrophil cytoplasmic antibodies (ANCA), or antistreptolysin O (ASO) titer should be carried out only when there is clinical evidence to specifically suggest an associated diagnosis, because these have poor predictive value when used for screening, especially when the pretest probability is low. For most of these, there is no value to repeated or serial serologic testing. Although 4–5% of a healthy population will have positive tests for RF and ANAs, only 1% and <0.4% of the population will have RA or SLE, respectively. IgM RF (autoantibodies against the Fc portion of IgG) is found in 80% of patients with RA and may also be seen in low titers in patients with chronic infections (tuberculosis, leprosy, hepatitis); other autoimmune diseases (SLE, Sjögren's syndrome); and chronic pulmonary, hepatic, or renal diseases. When considering RA, both serum RF and anti-CCP antibodies should be obtained as these are complementary. Both are comparably sensitive, but CCP antibodies are more specific than RF. In RA, the presence of anti-CCP and RF antibodies may indicate a greater risk for more severe, erosive polyarthritis. ANAs are found in nearly all patients with SLE and may also be seen in patients with other autoimmune diseases (polymyositis, systemic sclerosis, antiphospholipid syndrome, Sjögren's syndrome), drug-induced lupus (Table 18-2), chronic liver or renal disorders, and advanced age. Positive ANAs are found in 5% of adults and in up to 14% of elderly or chronically ill individuals. T e ANA test is very sensitive but poorly specific for lupus, as only 1–2% of all positive results will be caused by lupus alone. T e interpretation of a positive ANA test may depend on the magnitude of the titer and the pattern observed by immunofluorescence microscopy **(Table 18-4)**. Diffuse and speckled patterns are least specific, whereas a peripheral, or rim, pattern (related to autoantibodies against double-strand [native] DNA) is highly specific and suggestive of lupus. Centromeric patterns are seen in patients with limited cutaneous systemic sclerosis (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasia [CREST] syndrome) or primary biliary sclerosis, and nucleolar patterns may be seen in patients with diffuse cutaneous systemic sclerosis or inflammatory myositis.

Aspiration and analysis of synovial fluid are always indicated in acute monarthritis or when an infectious or crystal-induced arthropathy is suspected. Synovial

TABLE 18-4

ANTINUCLEAR ANTIBODY (ANA) PATTERNS AND CLINICAL ASSOCIATIONS

ANA PATTERN	ANTIGEN IDENTIFIED	CLINICAL CORRELATE
Dif use	Deoxyribonucleo-protein	Nonspecific
	Histones	Drug-induced lupus, lupus
Peripheral (rim)	ds-DNA	50% of SLE (specific)
Speckled	U1-RNP	>90% of MCTD
	Sm	30% of SLE (specific)
	Ro (SS-A)	Sjögren's 60%, SCLE, neonatal lupus, ANA(−) lupus
	La (SS-B)	50% of Sjögren's, 15% lupus
	Scl-70	40% of dif use cutaneous systemic sclerosis
	PM-1	Polymyositis (PM), dermatomyositis
	Jo-1	PM w/pneumonitis + arthritis
Nucleolar	RNA polymerase I, others	40% of dif use cutaneous systemic sclerosis
Centromere	Kinetochore	75% CREST (limited cutaneous systemic sclerosis)

Abbreviations: ANA, antinuclear antibody; CREST, calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia; MCTD, mixed connective tissue disease; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

fluid may distinguish between noninflammatory and inflammatory processes by analysis of the appearance, viscosity, and cell count. Tests for synovial fluid glucose, protein, lactate dehydrogenase, lactic acid, or autoantibodies are not recommended because they have no diagnostic value. Normal synovial fluid is clear or a pale straw color and is viscous, primarily because of the high levels of hyaluronate. Noninflammatory synovial fluid is clear, viscous, and amber-colored, with a WBC count of <2000/μL and a predominance of mononuclear cells. T e viscosity of synovial fluid is assessed by expressing fluid from the syringe one drop at a time. Normally, there is a stringing effect, with a long tail behind each synovial drop. Effusions caused by OA or trauma will have normal viscosity. Inflammatory fluid is turbid and yellow, with an increased WBC count (2000–50,000/μL) and a polymorphonuclear leukocyte predominance. Inflammatory fluid has reduced viscosity, diminished hyaluronate, and little or no tail following each drop of synovial fluid. Such effusions are found in RA, gout, and other inflammatory arthritides. Septic fluid is opaque and purulent, with a WBC count usually >50,000/μL, a predominance of polymorphonuclear leukocytes (>75%), and low viscosity. Such effusions are typical of septic arthritis but may also occur with RA or gout. In addition, hemorrhagic synovial fluid may be seen with trauma, hemarthrosis, or neuropathic arthritis. An algorithm for synovial fluid aspiration and analysis is shown in **Fig. 18-6**. Synovial fluid should be analyzed immediately for appearance, viscosity, and cell count. Monosodium urate crystals (observed in gout) are seen by polarized microscopy and are long, needle-shaped, negatively birefringent, and usually intracellular. In chondrocalcinosis and pseudogout, calcium pyrophosphate dihydrate crystals are usually

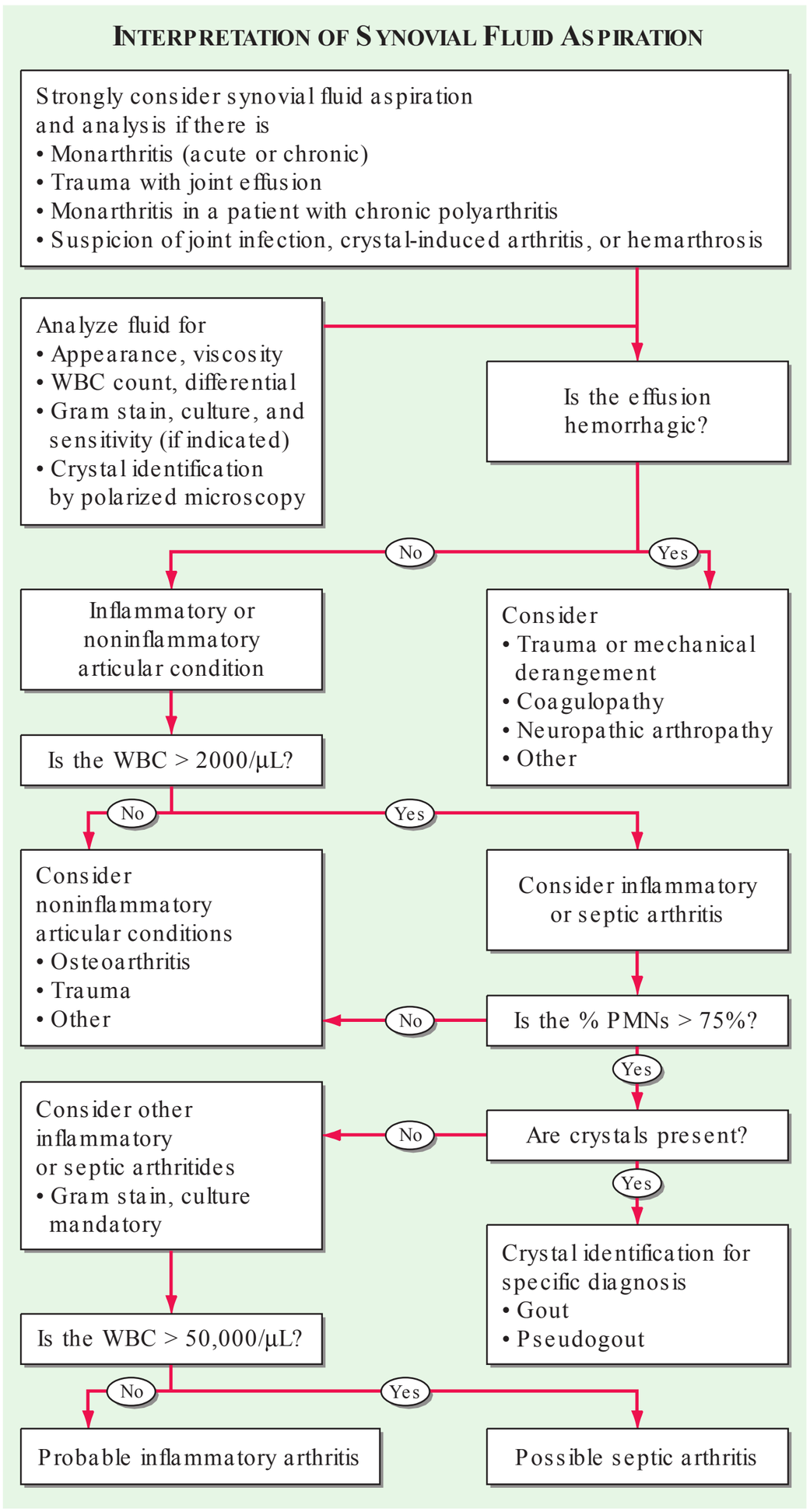


FIGURE 18-6

Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear (leukocytes); WBC, white blood cell (count).

short, rhomboid-shaped, and positively birefringent. Whenever infection is suspected, synovial fluid should be Gram stained and cultured appropriately. If gonococcal arthritis is suspected, nucleic acid amplification tests should be used to detect either Chlamydia trachomatis or N. gonorrhoeae infection. Synovial fluid from patients with chronic monarthritis should also be cultured for M. tuberculosis and fungi. Last, it should be noted that crystal-induced arthritis and septic arthritis occasionally occur together in the same joint.

DIAGNOSTIC IMAGING IN JOINT DISEASES

Conventional radiography has been a valuable tool in the diagnosis and staging of articular disorders. Plain x-rays are most appropriate and cost effective when there is a history of trauma, suspected chronic infection, progressive disability, or monarticular involvement; when therapeutic alterations are considered; or when a baseline assessment is desired for what appears to be a chronic process. However, in acute inflammatory arthritis, early radiography is rarely helpful in establishing a diagnosis and may only reveal soft tissue swelling or juxtaarticular demineralization. As the disease progresses, calcification (of soft tissues, cartilage, or bone), joint space narrowing, erosions, bony ankylosis, new bone formation (sclerosis, osteophytes, or periostitis), or subchondral cysts may develop and suggest specific clinical entities. Consultation with a radiologist will help define the optimal imaging modality, technique, or positioning and prevent the need for further studies.

Additional imaging techniques may possess greater diagnostic sensitivity and facilitate early diagnosis in a limited number of articular disorders and in selected circumstances and are indicated when conventional radiography is inadequate or nondiagnostic **(Table 18-5)**. Ultrasonography is useful in the detection of soft tissue abnormalities, such as tendinitis, tenosynovitis, enthesitis, bursitis, and entrapment neuropathies. Wider use, lower cost, better technology, and enhanced site-specific transducers now allow for routine use in outpatient care. Owing to low cost, portability, and wider use, ultrasound use has grown and is the preferred method for the evaluation of synovial (Baker's) cysts, rotator cuff tears, tendinitis and tendon injury, and crystal deposition on cartilage. Use of power Doppler allows for early detection of synovitis and bony erosions. Radionuclide scintigraphy is a very sensitive, but poorly specific, means of detecting inflammatory or metabolic alterations in bone or periarticular soft tissue structures. Scintigraphy is best suited for total-body assessment (extent and distribution) of skeletal

TABLE 18-5

DIAGNOSTIC IMAGING TECHNIQUES FOR MUSCULOSKELETAL DISORDERS

METHOD	IMAGING TIME, H	COST[a]	CURRENT INDICATIONS
Ultrasound	<1	++	Synovial (Baker's) cysts Rotator cuf tears Bursitis, tendinitis, tendon injury Enthesitis Carpal tunnel syndrome Urate or calcium pyrophosphate deposition on cartilage Early detection of synovial inflammation or erosions Ultrasound-guided injection/arthrocentesis
Radionuclide scintigraphy			
^{99m}Tc	1–4	++	Metastatic bone survey Evaluation of Paget's disease Identifying occult arthritis in patients with undiagnosed polyarthralgia
^{111}In-WBC	24	+++	Acute infection Prosthetic infection Acute osteomyelitis
^{67}Ga	24–48	++++	Acute and chronic infection Acute osteomyelitis
Computed tomography (CT)	<1	+++	Herniated intervertebral disk Sacroiliitis Spinal stenosis Spinal trauma Osteoid osteoma Stress fracture
Dual-energy CT	<1	NA	Uric acid deposition Tophus localization
Magnetic resonance imaging	1/2–2	++++	Avascular necrosis Osteomyelitis Septic arthritis, infected prosthetic joints Early sacroiliitis Intraarticular derangement and soft tissue injury Derangements of axial skeleton and spinal cord Herniated intervertebral disk Pigmented villonodular synovitis Inflammatory and metabolic muscle pathology

[a]Relative cost for imaging study.
Abbreviations: NA, not commercially available; WBC, white blood cell.

involvement (neoplasia, Paget's disease) and the assessment of patients with undiagnosed polyarthralgias, looking for occult arthritis. The use of scintigraphy has declined with greater use and declining cost of ultrasound and MRI. The limited tissue contrast resolution of scintigraphy may obscure the distinction between a bony or periarticular process and may necessitate the additional use of MRI. Scintigraphy using ^{99m}Tc, ^{67}Ga, or ^{111}In-labeled WBCs has been applied to a variety of articular disorders with variable success (Table 18-5). Although [^{99m}Tc] diphosphate scintigraphy may be useful in identifying osseous infection, neoplasia, inflammation, increased blood flow, bone remodeling, heterotopic bone formation, or avascular necrosis, MRI is preferred in most instances. Gallium scanning uses ^{67}Ga, which binds serum and cellular transferrin and lactoferrin and is preferentially taken up by neutrophils, macrophages, bacteria, and tumor tissue (e.g., lymphoma). As such, it is primarily used in the identification of occult infection or malignancy. Scanning with ^{111}In-labeled WBCs has been used to detect osteomyelitis and infectious or inflammatory arthritis. Despite their utility, ^{111}In-labeled WBC or ^{67}Ga scanning has largely been replaced by MRI, except when there is a suspicion of septic joint or prosthetic joint infections.

Computed tomography (CT) provides detailed visualization of the axial skeleton. Articulations previously considered difficult to visualize by radiography (e.g., zygapophyseal, sacroiliac, sternoclavicular, hip joints) can be effectively evaluated using CT. CT has been demonstrated to be useful in the diagnosis of low back pain syndromes (e.g., spinal stenosis vs herniated disk), sacroiliitis, osteoid osteoma, and stress fractures. Helical or spiral CT (with or without contrast angiography) is a novel technique that is rapid, cost effective, and sensitive in diagnosing pulmonary embolism or obscure fractures, often in the setting of initially equivocal findings. High-resolution CT can be advocated in the evaluation of suspected or established infiltrative lung disease (e.g., systemic sclerosis or rheumatoid lung). The recent use of hybrid (positron emission tomography [PET] or single-photon emission CT [SPECT]) CT scans in metastatic evaluations has incorporated CT to provide better anatomic localization of scintigraphic abnormalities. ^{18}F-Fluorodeoxyglucose (FDG) is the most commonly used radiopharmaceutical in PET scanning. FDG-PET/CT scans have been seldom used in the evaluation of septic or inflammatory arthritis. Dual-energy CT (DECT) scanning, developed in urology to identify urinary calculi, has been a highly sensitive and specific method used to identify and quantify uric acid deposition in tissues **(Fig. 18-7)**.

MRI has significantly advanced the ability to image musculoskeletal structures. MRI has the advantages of

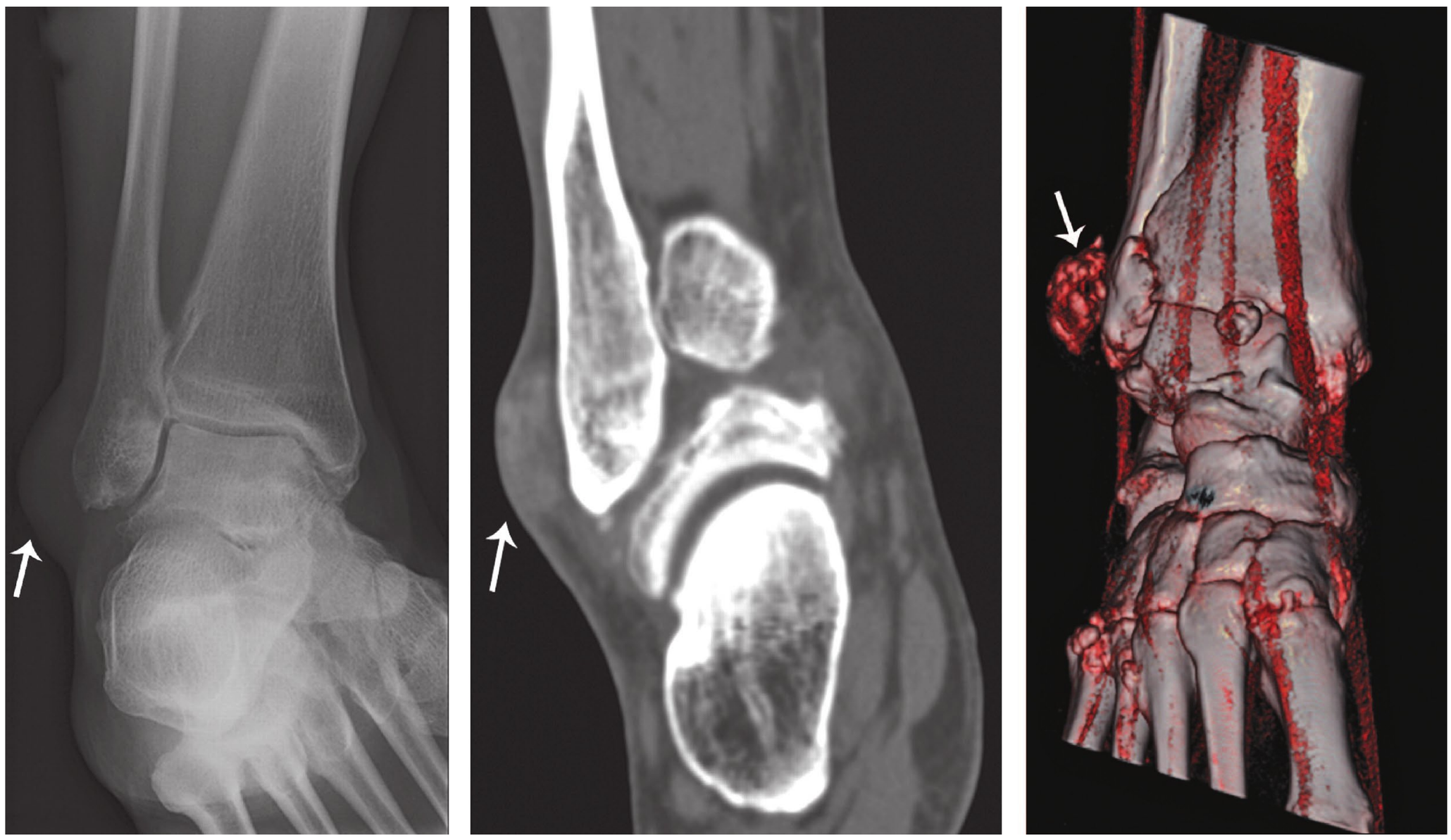


FIGURE 18-7

Dual-energy computed tomography (DECT) scan from a 45-year-old woman with right ankle swelling around the lateral malleolus. Three-dimensional volume-rendered coronal reformatted DECT image shows that the mass is composed of monosodium urate (red) in keeping with tophus (arrow). (Used with permission from S Nicolaou et al: AJR 194:1072, 2010.)

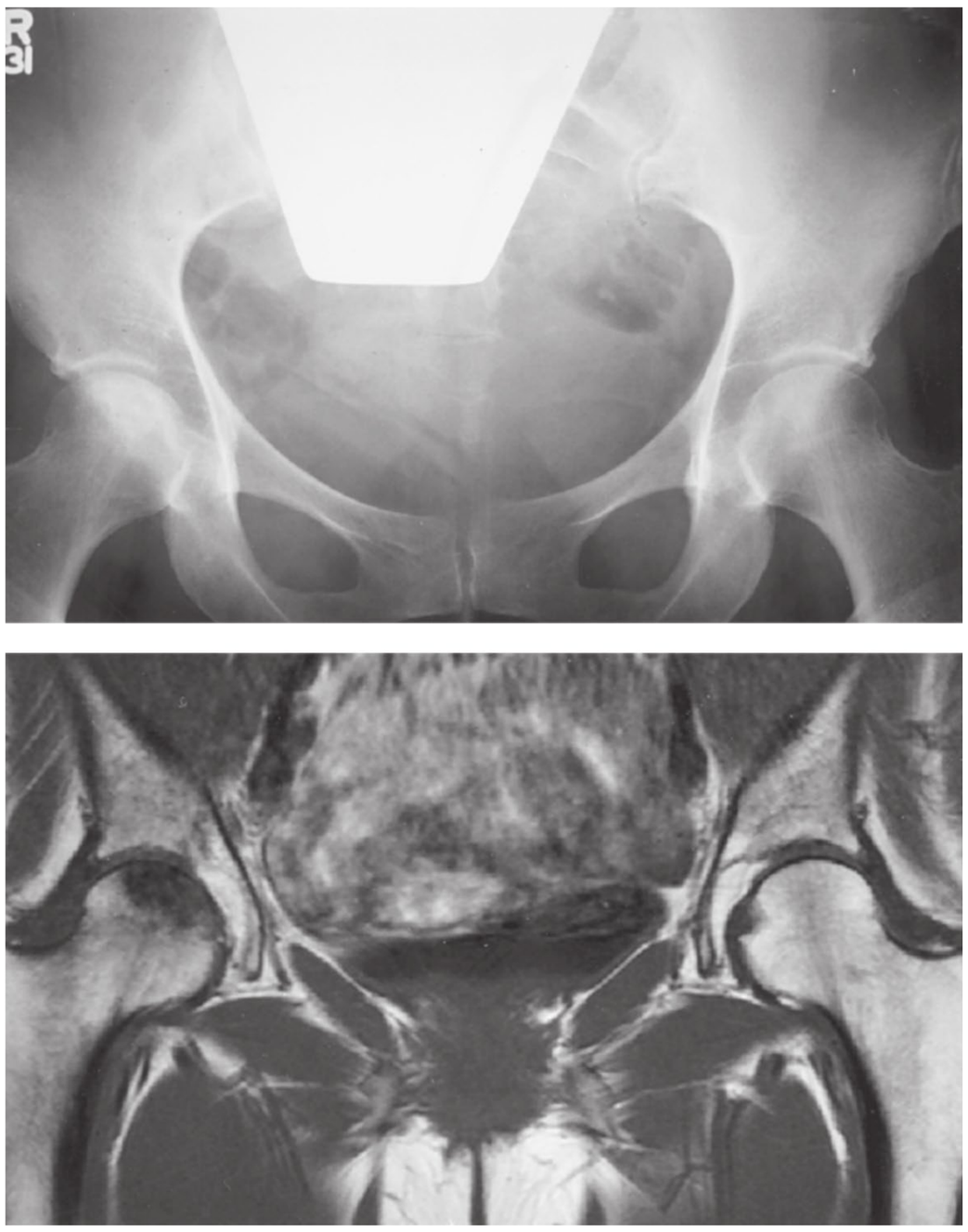


FIGURE 18-8
Superior sensitivity of magnetic resonance imaging (MRI) in the diagnosis of osteonecrosis of the femoral head. A 45-year-old woman receiving high-dose glucocorticoids developed right hip pain. Conventional x-rays (top) demonstrated only mild sclerosis of the right femoral head. T1-weighted MRI (bottom) demonstrated low-density signal in the right femoral head, diagnostic of osteonecrosis.

providing multiplanar images with fine anatomic detail and contrast resolution **(Fig. 18-8)** that allows for the superior ability to visualize bone marrow and soft tissue periarticular structures. Although more costly with a longer procedural time than CT, the MRI has become the preferred technique when evaluating complex musculoskeletal disorders.

MRI can image fascia, vessels, nerve, muscle, cartilage, ligaments, tendons, pannus, synovial effusions, and bone marrow. Visualization of particular structures can be enhanced by altering the pulse sequence to produce either T1- or T2-weighted spin echo, gradient echo, or inversion recovery (including short tau inversion recovery [STIR]) images. Because of its sensitivity to changes in marrow fat, MRI is a sensitive but nonspecific means of detecting osteonecrosis, osteomyelitis, and marrow inflammation indicating overlying synovitis or osteitis (Fig. 18-8). Because of its enhanced soft tissue resolution, MRI is more sensitive than arthrography or CT in the diagnosis of soft tissue injuries (e.g., meniscal and rotator cuff tears); intraarticular derangements; marrow abnormalities (osteonecrosis, myeloma); and spinal cord or nerve root damage, synovitis, or cartilage damage or loss.

Acknowledgment

The author acknowledges the contributions of Dr. Peter E. Lipsky to this chapter in previous editions.

CHAPTER 19

OSTEOARTHRITIS

David T. Felson

Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of OA is on the rise. In the United States, OA prevalence will increase by 66–100% by 2020.

OA affects certain joints, yet spares others **(Fig. 19-1)**. Commonly affected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (MTP). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Our joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips). Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses.

OA can be diagnosed based on structural abnormalities or on the symptoms these abnormalities evoke. According to cadaveric studies, by elderly years, structural changes of OA are nearly universal. T ese include cartilage loss (seen as joint space loss on x-rays) and osteophytes. Many persons with x-ray evidence of OA have no joint symptoms, and although the prevalence of structural abnormalities is of interest in understanding disease pathogenesis, what matters more from a clinical perspective is the prevalence of symptomatic OA. Symptoms, usually joint pain, determine disability, visits to clinicians, and disease costs.

Symptomatic OA of the knee (pain on most days of a recent month in a knee plus x-ray evidence of OA in that knee) occurs in ~12% of persons age ≥60 in the United States and 6% of all adults age ≥30. Symptomatic hip OA is roughly one-third as common as disease in the knee. Although radiographically evident hand OA and the appearance of bony enlargement in affected hand joints **(Fig. 19-2)** are extremely common in older persons, most cases are often not symptomatic. Even so, symptomatic hand OA occurs in ~10% of elderly individuals and often produces measurable limitation in function.

T e prevalence of OA rises strikingly with age. Regardless of how it is defined, OA is uncommon in adults under age 40 and highly prevalent in those over age 60. It is also a disease that, at least in middle-aged and elderly persons, is much more common in women

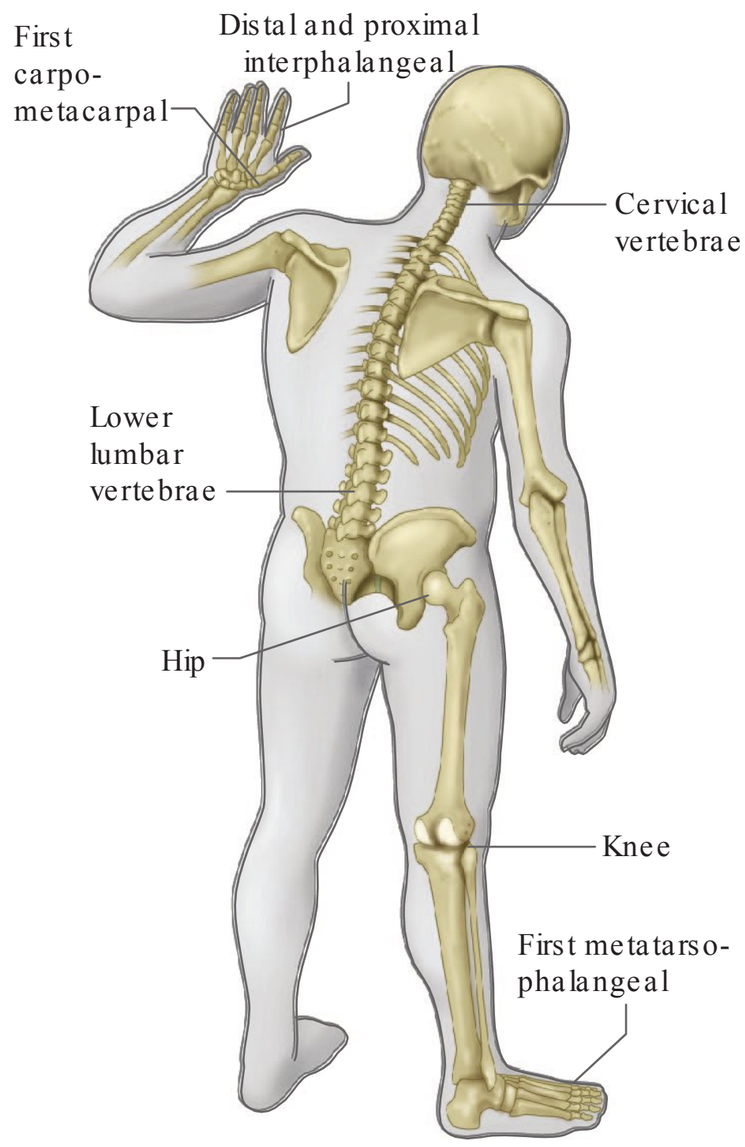


FIGURE 19-1
Joints commonly af ected by osteoarthritis.



FIGURE 19-2
Severe osteoarthritis of the hands affecting the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bouchard's nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base.

than in men, and sex differences in prevalence increase with age.

X-ray evidence of OA is common in the lower back and neck, but back pain and neck pain have not been tied to findings of OA on x-ray. Thus, back pain and neck pain are treated separately.

DEFINITION

OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic sine qua non of disease is hyaline articular cartilage loss, present in a focal and, initially, nonuniform manner. This is accompanied by increasing thickness and sclerosis of the subchondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by mild synovitis in many affected joints, and by weakness of muscles bridging the joint. In knees, meniscal degeneration is part of the disease. There are numerous pathways that lead to joint failure, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

JOINT PROTECTIVE MECHANISMS AND THEIR FAILURE

Joint protectors include joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion.

Synovial fluid reduces friction between articulating cartilage surfaces, thereby serving as a protector against friction-induced cartilage wear. Its lubrication function depends on hyaluronic acid and on lubricin, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation.

The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory afferent nerves. These mechanoreceptors fire at different frequencies throughout a joint's range of motion, providing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons can assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading.

Muscles and tendons that bridge the joint are key joint protectors. Their coordinated contractions at the appropriate time in joint movement provide the appropriate power and acceleration for the limb to accomplish its tasks. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface.

Failure of these joint protectors increases the risk of joint injury and OA. For example, in animals, OA develops rapidly when a sensory nerve to the joint is sectioned and joint injury induced. Similarly, in humans, Charcot's arthropathy, a severe and rapidly progressive OA, develops when minor joint injury occurs in the presence of posterior column peripheral neuropathy. Another example of joint protector failure is rupture of ligaments, a well-known cause of the early development of OA.

CARTILAGE AND ITS ROLE IN JOINT FAILURE

In addition to being a primary target tissue for disease, cartilage also functions as a joint protector. A thin rim of tissue at the ends of two opposing bones, cartilage is lubricated by synovial fluid to provide an almost frictionless surface across which these two bones move. The compressible stiffness of cartilage compared to bone provides the joint with impact-absorbing capacity.

The earliest changes of OA may occur in cartilage, and abnormalities there can accelerate disease development. The two major macromolecules in cartilage are type 2 collagen, which provides cartilage its tensile strength, and aggrecan, a proteoglycan macromolecule linked with hyaluronic acid, which consists of highly negatively charged glycosaminoglycans. In normal cartilage, type 2 collagen is woven tightly, constraining the aggrecan molecules in the interstices between collagen strands, forcing these highly negatively charged

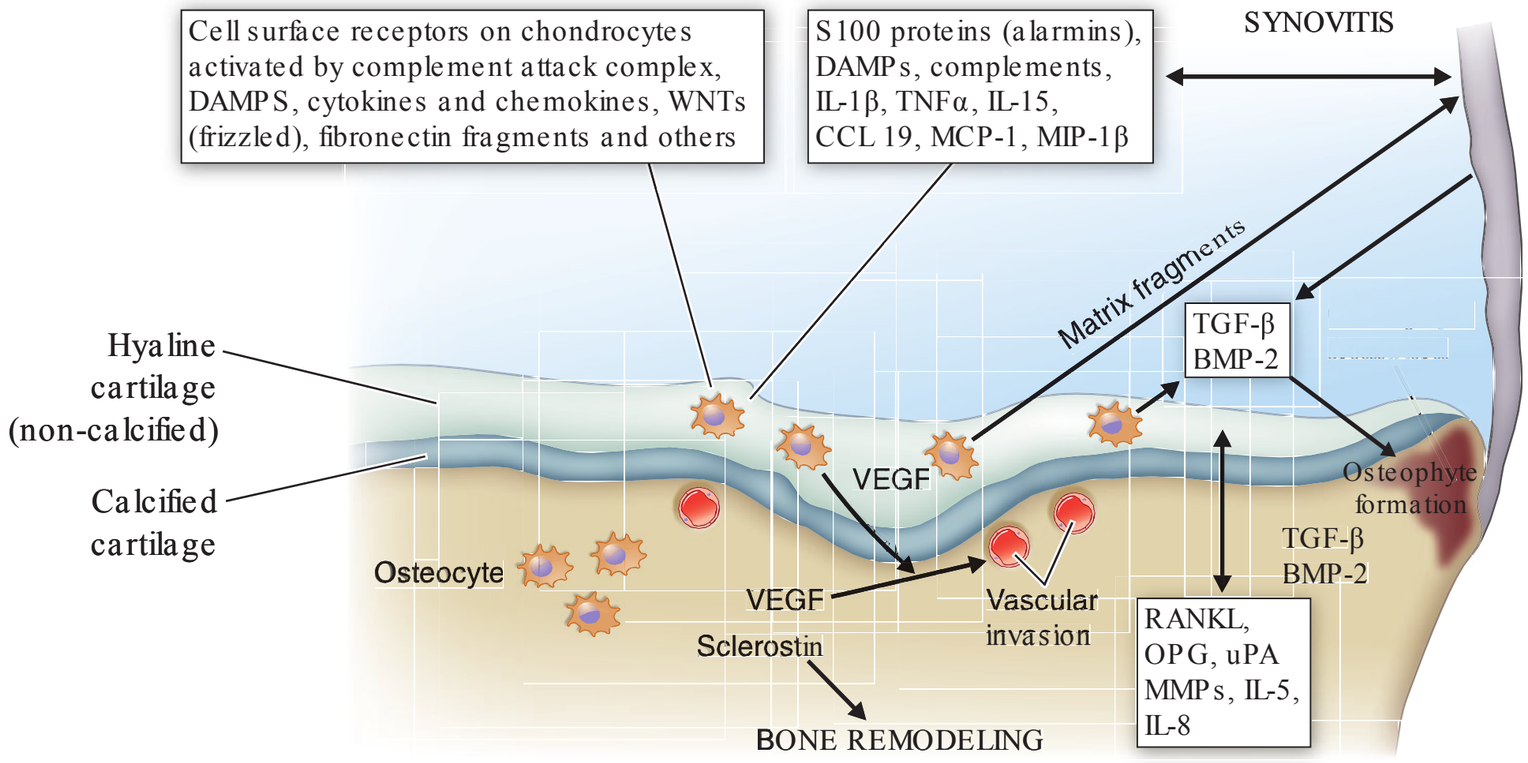


FIGURE 19-3

Selected factors involved in the osteoarthritic process including chondrocytes, bone, and synovium. Synovitis causes release of cytokines, alarmins, damage-associated molecular pattern (DAMP) molecules, and complement, which activate chondrocytes through cell surface receptors. Chondrocytes produce matrix molecules (collagen type 2, aggrecan) and the enzymes responsible for the degradation of the matrix (e.g., ADAMTS-5 and matrix metalloproteinases [MMPs]). Bone invasion occurs through the calcified cartilage, triggered by vascular endothelial growth factor (VEGF) and other molecules. IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor. (From RF Loeser et al: Arthritis Rheum 64:1697, 2012.)

molecules into close proximity with one another. The aggrecan molecule, through electrostatic repulsion of its negative charges, gives cartilage its compressive stiffness. Chondrocytes, the cells within this avascular tissue, synthesize all elements of the matrix and produce enzymes that break down the matrix. Synovium and chondrocytes synthesize and release cytokines and growth factors, which provide feedback that modulates synthesis of matrix molecules **(Fig. 19-3)**. Cartilage matrix synthesis and catabolism are in a dynamic equilibrium influenced by the cytokine and growth factor environment. Mechanical and osmotic stress on chondrocytes induces these cells to alter gene expression and increase production of inflammatory cytokines and matrix-degrading enzymes. While chondrocytes synthesize numerous enzymes, matrix metalloproteinases (MMP) (especially collagenases and ADAMTS-5) are critical enzymes in the breakdown of cartilage matrix. Both collagenase and aggrecanases act primarily in the territorial matrix surrounding chondrocytes; however, as the osteoarthritic process develops, their activities and effects spread throughout the matrix, especially in the superficial layers of cartilage.

The synovium, cartilage, and bone all influence disease development through cytokines, chemokines, and even complement activation (Fig. 19-3). These act on chondrocyte cell surface receptors and ultimately have transcriptional effects. Matrix fragments released from cartilage stimulate synovitis. Among the most important cytokines are interleukin (IL) 1β, which exerts transcriptional effects on chondrocytes, stimulating production of proteinases and suppressing cartilage matrix synthesis. Tumor necrosis factor (TNF) α may play a similar role to that of IL-1. These cytokines also induce chondrocytes to synthesize prostaglandin E_2 and nitric oxide, which have complex effects on matrix synthesis and degradation. At early stages in the matrix response to injury and in the healthy response to loading, the net effect of cytokine stimulation may be matrix synthesis, but ultimately, the combination of effects on chondrocytes triggers matrix degradation. Enzymes in the matrix are held in check by activation inhibitors, including tissue inhibitor of metalloproteinase (TIMP). Growth factors are also part of this complex network, with BMP-2 and transforming growth factor β playing prominent roles in stimulating the development of osteophytes. Whereas healthy articular cartilage is avascular in part due to angiogenesis inhibitors present in cartilage, disease is characterized by the invasion of blood vessels into cartilage from underlying bone and proliferation of vessels within synovium. This is influenced by vascular endothelial growth factor (VEGF) synthesis in the cartilage and bone. With these blood vessels come nerves that may bring nociceptive innervation.

Probably as a result of chronic oxidative damage, articular chondrocytes exhibit an age-related decline in synthetic capacity while maintaining the ability to produce proinflammatory mediators and matrix-degrading enzymes, findings characteristic of a senescent secretory phenotype. These chondrocytes are unable to maintain tissue homeostasis (such as after insults of a

mechanical or inflammatory nature). T us, with age, cartilage is easily damaged by minor sometimes unnoticed injuries, including those that are part of daily activities.

OA cartilage is characterized by gradual depletion of aggrecan, an unfurling of the tightly woven collagen matrix, and loss of type 2 collagen. With these changes comes increasing vulnerability of cartilage, which loses its compressive stiffness.

RISK FACTORS

Joint vulnerability and joint loading are the two major factors contributing to the development of OA. On the one hand, a vulnerable joint whose protectors are dysfunctional can develop OA with minimal levels of loading, perhaps even levels encountered during everyday activities. On the other hand, in a young joint with competent protectors, a major acute injury or long-term overloading is necessary to precipitate disease. Risk factors for OA can be understood in terms of their effect either on joint vulnerability or on loading **(Fig. 19-4)**.

SYSTEMIC RISK FACTORS

Age is the most potent risk factor for OA. Radiographic evidence of OA is rare in individuals under age 40; however, in some joints, such as the hands, OA occurs in >50% of persons over age 70. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates cartilage matrix synthesis by chondrocytes in young cartilage, aged cartilage is less responsive to these stimuli. Partly because of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress at basal layers and is at greater risk of cartilage damage. Also, joint protectors fail more often with age. Muscles that bridge the joint become weaker with age and also respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. T ese factors work in concert to increase the vulnerability of older joints to OA.

Older women are at high risk of OA in all joints, a risk that emerges as women reach their sixth decade. Although hormone loss with menopause may contribute to this risk, there is little understanding of the unique vulnerability of older women versus men to OA.

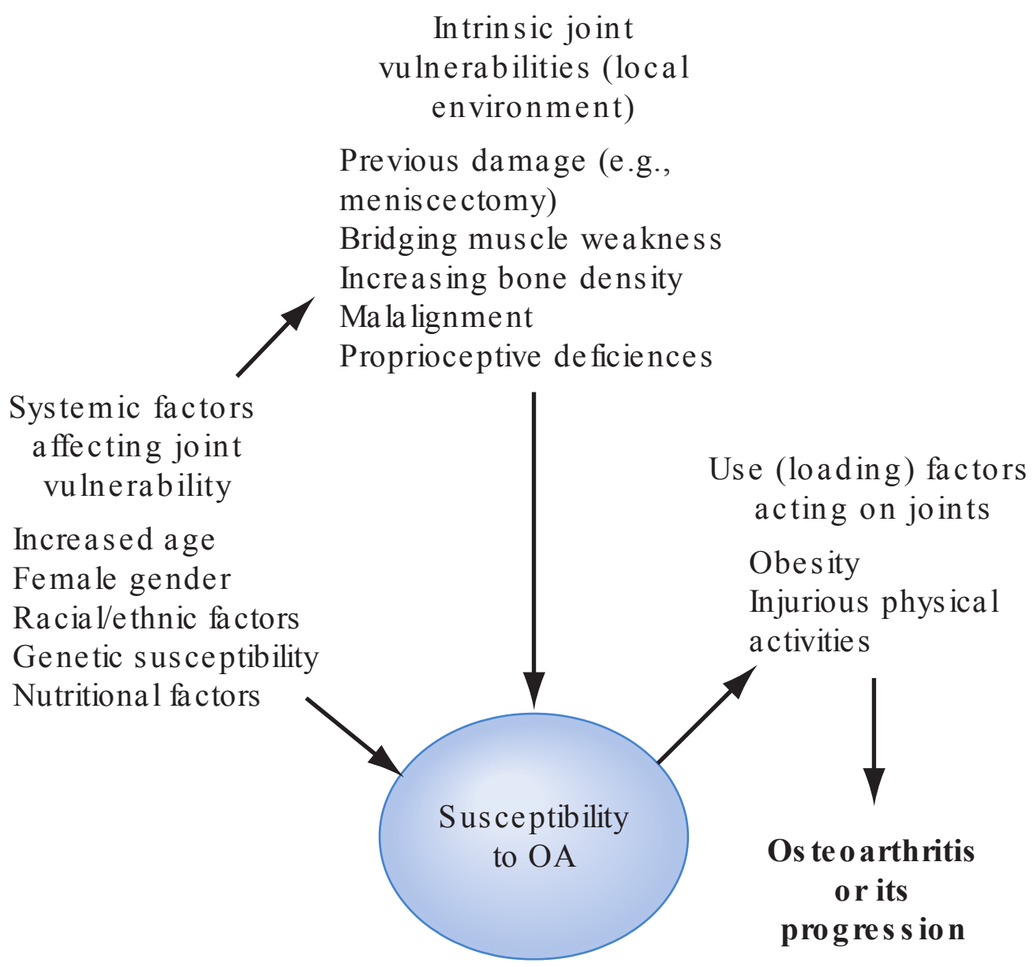


FIGURE 19-4

Risk **f**actors **f**or osteoarthritis (OA) either contribute to the susceptibility of the joint (systemic factors or factors in the local joint environment) or increase risk by the load they put on the joint. Usually a combination of loading and susceptibility factors is required to cause disease or its progression.

HERITABILITY AND GENETICS

OA is a highly heritable disease, but its heritability is joint specific. Fifty percent of the hand and hip OA in the community is attributable to inheritance, i.e., to disease present in other members of the family. However, the heritable proportion of knee OA is at most 30%, with some studies suggesting no heritability at all. Whereas many people with OA have disease in multiple joints, this "generalized OA" phenotype is rarely inherited and is more often a consequence of aging.

Emerging evidence has identified genetic mutations that confer a high risk of OA, the best replicated is a polymorphism within the growth differentiation factor 5 gene. T is polymorphism diminishes the quantity of GDF5; GDF5 has its main influence on joint shape, and genes predisposing to OA are likely to increase risk of disease based on their effects on joint development and shape.

GLOBAL CONSIDERATIONS



Hip OA is rare in China and in immigrants from China to the United States. However, OA in the knees is at least as common, if not more so, in Chinese than in whites from the United States, and knee OA represents a major cause of disability in China, especially in rural areas. Anatomic differences between Chinese and white hips may account for much of the difference in hip OA prevalence, with white hips having a higher prevalence of anatomic predispositions to the development of OA. Persons from Africa, but not African Americans, may also have a very low rate of hip OA.

RISK FACTORS IN THE JOINT ENVIRONMENT

Some risk factors increase vulnerability of the joint through local effects on the joint environment. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or in childhood, congenital dysplasia, Legg-Perthes disease, and slipped capital femoral epiphysis, leave a child with distortions of hip joint anatomy that often lead to OA later in life. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dislocation, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood (severe abnormalities) or middle age (mild abnormalities).

Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is otherwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA.

Tears of ligamentous and fibrocartilaginous structures that protect the joints, such as the anterior cruciate ligament and the meniscus in the knee and the labrum in the hip, can lead to premature OA. Meniscal tears increase with age and when chronic are often asymptomatic but lead to adjacent cartilage damage and accelerated OA. Even injuries in which the affected person never received a diagnosis may increase risk of OA. For example, in the Framingham Study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA.

Another source of anatomic abnormality is malalignment across the joint **(Fig. 19-5)**. T is factor has been best studied in the knee, which is the fulcrum of the longest lever arm in the body. Varus (bowlegged) knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the knee, whereas valgus (knock-kneed) malalignment predisposes to rapid cartilage loss in the lateral compartment. Malalignment causes this effect by increasing stress on a focal area of cartilage, which then breaks down. T ere is evidence that malalignment in the knee not only causes cartilage loss but leads to underlying bone damage, producing bone marrow lesions seen on magnetic resonance imaging (MRI). Malalignment in the knee often produces such a substantial increase in focal stress within the knee (as evidenced by its destructive effects on subchondral bone) that severely malaligned knees may be destined to progress regardless of the status of other risk factors.

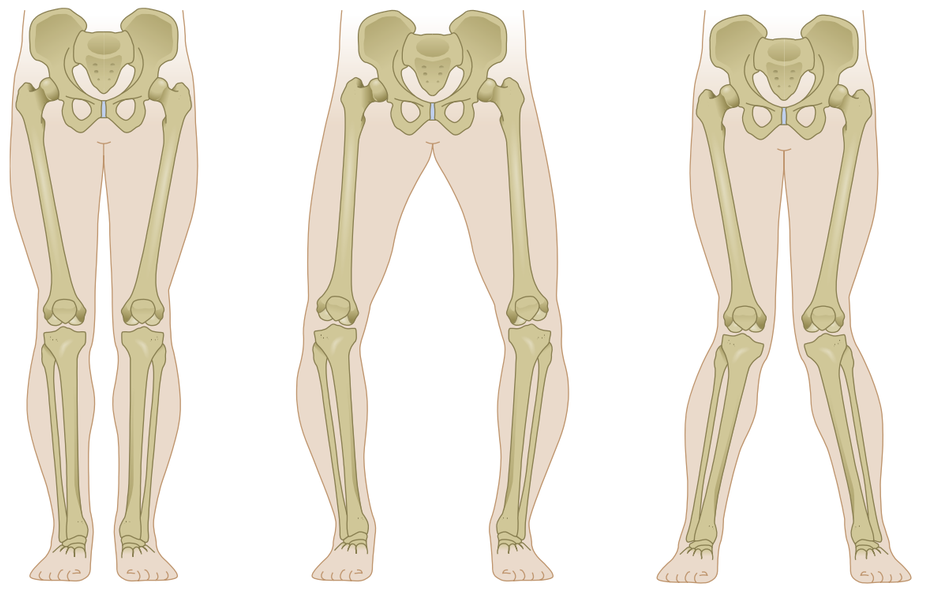


FIGURE 19-5
The two types of limb malalignment in the frontal plane: varus, in which the stress is placed across the medial compartment of the knee joint, and valgus, which places excess stress across the lateral compartment of the knee.

Weakness in the quadriceps muscles bridging the knee increases the risk of the development of painful OA in the knee.

Patients with knee OA have impaired proprioception across their knees, and this may predispose them to further disease progression. T e role of bone in serving as a shock absorber for impact load is not well understood, but persons with increased bone density are at high risk of OA, suggesting that the resistance of bone to impact during joint use may play a role in disease development.

LOADING FACTORS

Obesity

T ree to six times body weight is transmitted across the knee during single-leg stance. Any increase in weight may be multiplied by this factor to reveal the excess force across the knee in overweight persons during walking. Obesity is a well-recognized and potent risk factor for the development of knee OA and, less so, for hip OA. Obesity precedes the development of disease and is not just a consequence of the inactivity present in those with disease. It is a stronger risk factor for disease in women than in men, and in women, the relationship of weight to the risk of disease is linear, so that with each increase in weight, there is a commensurate increase in risk. Weight loss in women lowers the risk of developing symptomatic disease. Not only is obesity a risk factor for OA in weight-bearing joints, but obese persons have more severe symptoms from the disease.

Obesity's effect on the development and progression of disease is mediated mostly through the increased loading in weight-bearing joints that occurs in overweight persons. However, a modest association of obesity with an increased risk of hand OA suggests that

there may be a systemic metabolic factor circulating in obese persons that affects disease risk also.

Repeated Use of Joint and Exercise

There are two categories of repetitive joint use, occupational use and leisure time physical activities. Workers performing repetitive tasks as part of their occupations for many years are at high risk of developing OA in the joints they use repeatedly. For example, farmers are at high risk for hip OA, and miners have high rates of OA in knees and spine. Workers whose jobs require regular knee bending or lifting or carrying heavy loads have a high rate of knee OA. One reason why workers may get disease is that during long days at work, their muscles may gradually become exhausted, no longer serving as effective joint protectors.

It is widely recommended for people to adopt an exercise-filled lifestyle, and long-term studies of exercise suggest no consistent association of exercise with OA risk in the majority of persons. However, persons who already have injured joints may put themselves at greater risk by engaging in certain types of exercise. For example, persons who have already sustained major knee injuries are at increased risk of progressive knee OA as a consequence of running. In addition, compared to nonrunners, elite runners (professional runners and those on Olympic teams) have high risks of both knee and hip OA. Lastly, although recreational runners are not at increased risk of knee OA, studies suggest that they have a modest increased risk of disease in the hip.

PATHOLOGY

The pathology of OA provides evidence of the involvement of many joint structures in disease. Cartilage initially shows surface fibrillation and irregularity. As disease progresses, focal erosions develop there, and these eventually extend down to the subjacent bone. With further progression, cartilage erosion down to bone expands to involve a larger proportion of the joint surface, even though OA remains a focal disease with nonuniform loss of cartilage **(Fig. 19-6)**.

After an injury to cartilage, chondrocytes undergo mitosis and clustering. Although the metabolic activity of these chondrocyte clusters is high, the net effect of this activity is to promote proteoglycan depletion in the matrix surrounding the chondrocytes. This is because the catabolic is greater than the synthetic activity. As disease develops, collagen matrix becomes damaged, the negative charges of proteoglycans get exposed, and cartilage swells from ionic attraction to water molecules. Because in damaged cartilage proteoglycans are no longer forced into close proximity, cartilage does not bounce back after loading as it did when healthy, and cartilage becomes vulnerable to further injury. Chondrocytes at the basal level of cartilage undergo apoptosis.

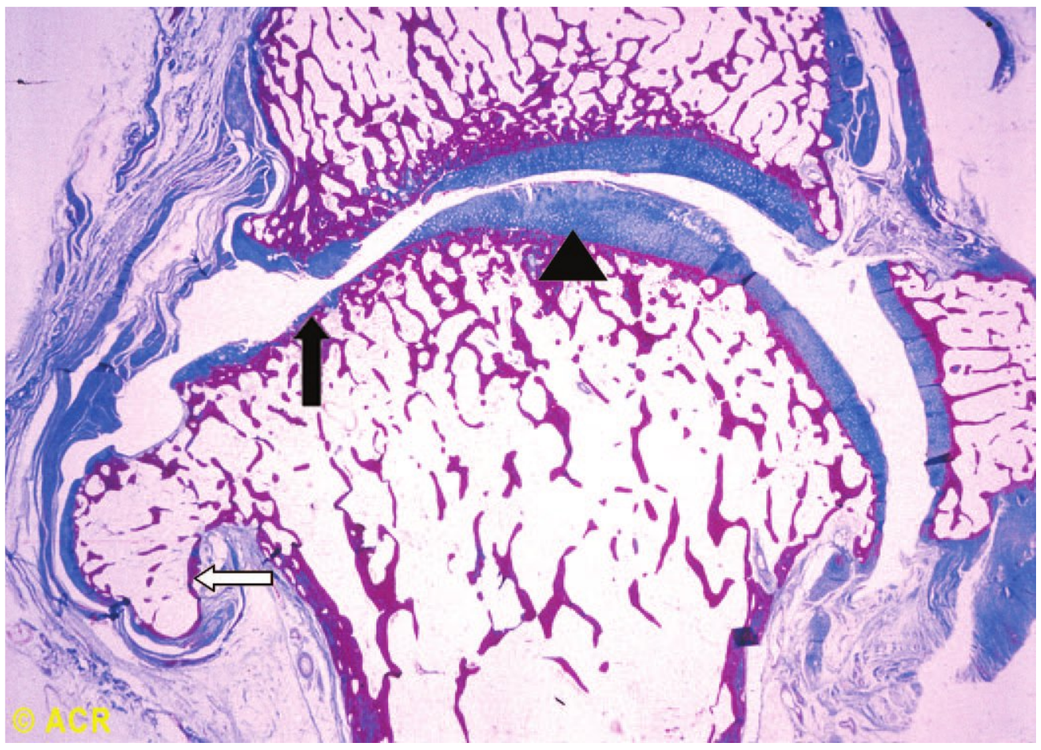


FIGURE 19-6
Pathologic changes of osteoarthritis in a toe joint. Note the nonuniform loss of cartilage (arrowhead vs solid arrow), the increased thickness of the subchondral bone envelope (solid arrow), and the osteophyte (open arrow). (From the American College of Rheumatology slide collection.)

With loss of cartilage come alterations in subchondral bone. Stimulated by growth factors and cytokines, osteoclasts and osteoblasts in the subchondral bony plate, just underneath cartilage, become activated. Bone formation produces a thickening and stiffness of the subchondral plate that occurs even before cartilage ulcerates. Trauma to bone during joint loading may be the primary factor driving this bone response, with healing from injury (including microcracks) producing stiffness. Small areas of osteonecrosis usually exist in joints with advanced disease. Bone death may also be caused by bone trauma with shearing of microvasculature, leading to a cutoff of vascular supply to some bone areas.

At the margin of the joint, near areas of cartilage loss, osteophytes form. These start as outgrowths of new cartilage, and with neurovascular invasion from the bone, this cartilage ossifies. Osteophytes are an important radiographic hallmark of OA. In malaligned joints, osteophytes grow larger on the side of the joint subject to most loading stress (e.g., in varus knees, osteophytes grow larger on the medial side).

The synovium produces lubricating fluids that minimize shear stress during motion. In healthy joints, the synovium consists of a single discontinuous layer filled with fat and containing two types of cells, macrophages and fibroblasts, but in OA, it can sometimes become edematous and inflamed. There is a migration of macrophages from the periphery into the tissue, and

cells lining the synovium proliferate. Enzymes secreted by the synovium digest cartilage matrix that has been released from the surface of the cartilage.

Additional pathologic changes occur in the capsule, which stretches, becomes edematous, and can become fibrotic.

T e pathology of OA is not identical across joints. In hand joints with severe OA, for example, there are often cartilage erosions in the center of the joint probably produced by bony pressure from the opposite side of the joint.

Basic calcium phosphate and calcium pyrophosphate dihydrate crystals are present microscopically in most joints with end-stage OA. T eir role in osteoarthritic cartilage is unclear, but their release from cartilage into the joint space and joint fluid likely triggers synovial inflammation, which can, in turn, produce release of enzymes and trigger nociceptive stimulation.

SOURCES OF PAIN

Because cartilage is aneural, cartilage loss in a joint is not accompanied by pain. T us, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by the x-ray, and the severity of x-ray changes in OA correlates poorly with pain severity.

Based on MRI studies in osteoarthritic knees comparing those with and without pain and on studies mapping tenderness in unanesthetized joints, likely sources of pain include synovial inflammation, joint effusions, and bone marrow edema. Modest synovitis develops in many but not all osteoarthritic joints. Some diseased joints have no synovitis, whereas others have synovial inflammation that approaches the severity of joints with rheumatoid arthritis **(Chap. 6)**. T e presence of synovitis on MRI is correlated with the presence and severity of knee pain. Capsular stretching from fluid in the joint stimulates nociceptive fibers there, inducing pain. Increased focal loading as part of the disease not only damages cartilage but probably also injures the underlying bone. As a consequence, bone marrow edema appears on the MRI; histologically, this edema signals the presence of microcracks and scar, which are the consequences of trauma. T ese lesions may stimulate bone nociceptive fibers. Also, hemostatic pressure within bone rises in OA, and the increased pressure itself may stimulate nociceptive fibers, causing pain.

Pain may arise from outside the joint also, including bursae near the joints. Common sources of pain near the knee are anserine bursitis and iliotibial band syndrome.

Persons with chronic OA pain may develop nervous system alterations as a consequence of disease, changes which decrease inhibitory controls on nociception and its distribution. T is may produce allodynia and hyperalgesia in some patients with OA.

CLINICAL FEATURES

Joint pain from OA is activity-related. Pain comes on either during or just after joint use and then gradually resolves. Examples include knee or hip pain with going up or down stairs, pain in weight-bearing joints when walking, and, for hand OA, pain when cooking. Early in disease, pain is episodic, triggered often by a day or two of overactive use of a diseased joint, such as a person with knee OA taking a long run and noticing a few days of pain thereafter. As disease progresses, the pain becomes continuous and even begins to be bothersome at night. Stiffness of the affected joint may be prominent, but morning stiffness is usually brief (<30 min).

In knees, buckling may occur, in part, due to weakness of muscles crossing the joint. Mechanical symptoms, such as buckling, catching, or locking, could also signify internal derangement, such as meniscal tears, and need to be evaluated. In the knee, pain with activities requiring knee flexion, such as stair climbing and arising from a chair, often emanates from the patellofemoral compartment of the knee, which does not actively articulate until the knee is bent ~35°.

OA is the most common cause of chronic knee pain in persons over age 45, but the differential diagnosis is long. Inflammatory arthritis is likely if there is prolonged morning stiffness and many other joints are affected. Bursitis occurs commonly around knees and hips. A physical examination should focus on whether tenderness is over the joint line (at the junction of the two bones around which the joint is articulating) or is outside of it. Anserine bursitis, medial and distal to the knee, is an extremely common cause of chronic knee pain that may respond to a glucocorticoid injection. Prominent nocturnal pain in the absence of end-stage OA merits a distinct workup. For hip pain, OA can be detected by loss of internal rotation on passive movement, and pain isolated to an area lateral to the hip joint usually reflects the presence of trochanteric bursitis.

No blood tests are routinely indicated for workup of patients with OA unless symptoms and signs suggest inflammatory arthritis. Examination of the synovial fluid is often more helpful diagnostically than an x-ray. If the synovial fluid white count is >1000/μL, inflammatory arthritis or gout or pseudogout is likely, the latter two being also identified by the presence of crystals.

X-rays are indicated to evaluate chronic hand pain and hip pain thought to be due to OA, as the diagnosis

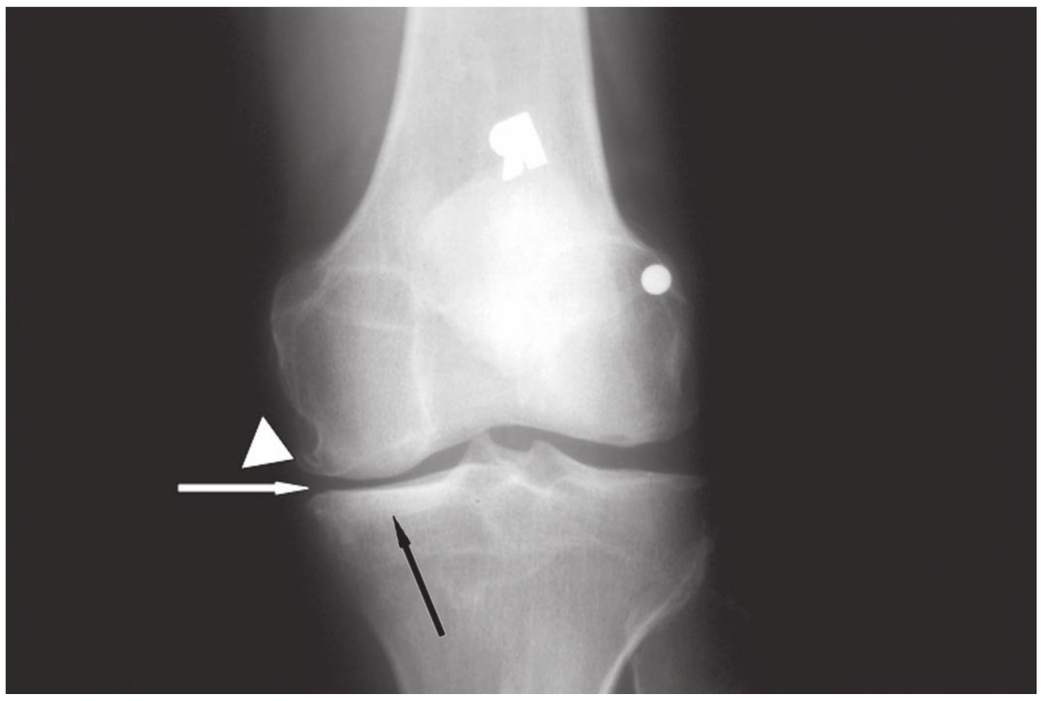


FIGURE 19-7
X-ray of knee with medial osteoarthritis. Note the narrowed joint space on medial side of the joint only (white arrow), the sclerosis of the bone in the medial compartment providing evidence of cortical thickening (black arrow), and the osteophytes in the medial femur (white wedge).

is often unclear without confirming radiographs. For knee pain, x-rays should be obtained if symptoms or signs are not typical of OA or if knee pain persists after inauguration of effective treatment. In OA, radiographic findings **(Fig. 19-7)** correlate poorly with the presence and severity of pain. Further, radiographs may be normal in early disease as they are insensitive to cartilage loss and other early findings.

Although MRI may reveal the extent of pathology in an osteoarthritic joint, it is not indicated as part of the diagnostic workup. Findings such as meniscal tears and cartilage and bone lesions occur in most patients with OA in the knee, but almost never warrant a change in therapy.

TREATMENT Osteoarthritis

The goals of the treatment of OA are to alleviate pain and minimize loss of physical function. To the extent that pain and loss of function are consequences of inflammation, of weakness across the joint, and of laxity and instability, the treatment of OA involves addressing each of these impairments. Comprehensive therapy consists of a multimodality approach including nonpharmacologic and pharmacologic elements.

Patients with mild and intermittent symptoms may need only reassurance or nonpharmacologic treatments. Patients with ongoing, disabling pain are likely to need both nonpharmacotherapy and pharmacotherapy.

Treatments for knee OA have been more completely evaluated than those for hip and hand OA or for disease in other joints. Thus, although the principles of treatment are identical for OA in all joints, we shall focus below on the treatment of knee OA, noting specific recommendations for disease in other joints, especially when they differ from those for the knee.

NONPHARMACOTHERAPY Because OA is a mechanically driven disease, the mainstay of treatment involves altering loading across the painful joint and improving the function of joint protectors, so they can better distribute load across the joint. Ways of lessening focal load across the joint include:

1. avoiding activities that overload the joint, as evidenced by their causing pain;
2. improving the strength and conditioning of muscles that bridge the joint, so as to optimize their function; and
3. unloading the joint, either by redistributing load within the joint with a brace or a splint or by unloading the joint during weight bearing with a cane or a crutch.

The simplest effective treatment for many patients is to avoid activities that precipitate pain. For example, for the middle-aged patient whose long-distance running brings on symptoms of knee OA, a less demanding form of weight-bearing activity may alleviate all symptoms. For an older person whose daily constitutionals up and down hills bring on knee pain, routing the constitutional away from hills might eliminate symptoms.

Each pound of weight increases the loading across the knee three- to sixfold. Weight loss may have a commensurate multiplier effect, unloading both knees and hips and probably relieving pain in those joints.

In hand joints affected by OA, splinting, by limiting motion, often minimizes pain for patients with involvement especially in the base of the thumb. Weight-bearing joints such as knees and hips can be unloaded by using a cane in the hand opposite to the affected joint for partial weight bearing. A physical therapist can help teach the patient how to use the cane optimally, including ensuring that its height is optimal for unloading. Crutches or walkers can serve a similar beneficial function.

Exercise Osteoarthritic pain in knees or hips during weight bearing results in lack of activity and poor mobility, and because OA is so common, the inactivity that results represents a public health concern, increasing the risk of cardiovascular disease and obesity. Aerobic capacity is poor in most elders with symptomatic knee OA, worse than others of the same age.

Weakness in muscles that bridge osteoarthritic joints is multifactorial in etiology. First, there is a decline in strength with age. Second, with limited mobility comes disuse muscle atrophy. Third, patients with painful knee or hip OA alter their gait so as to lessen loading across the affected joint, and this further diminishes muscle use. Fourth, "arthrogenous inhibition" may occur, whereby contraction of muscles bridging the joint is inhibited by a nerve afferent feedback loop emanating in a swollen and stretched joint capsule; this prevents maximal attainment of voluntary maximal strength.

Because adequate muscle strength and conditioning are critical to joint protection, weakness in a muscle that bridges a diseased joint makes the joint more susceptible to further damage and pain. T e degree of weakness correlates strongly with the severity of joint pain and the degree of physical limitation. One of the cardinal elements of the treatment of OA is to improve the functioning of muscles surrounding the joint.

For knee and hip OA, trials have shown that exercise lessens pain and improves physical function. Most effective exercise regimens consist of aerobic and/or resistance training, the latter of which focuses on strengthening muscles across the joint. Exercises are likely to be effective, especially if they train muscles for the activities a person performs daily. Activities that increase pain in the joint should be avoided, and the exercise regimen needs to be individualized to optimize effectiveness. Range-of-motion exercises, which do not strengthen muscles, and isometric exercises that strengthen muscles, but not through range of motion, are unlikely to be effective by themselves. Low-impact exercises, including water aerobics and water resistance training, are often better tolerated by patients than exercises involving impact loading, such as running or treadmill exercises. A patient should be referred to an exercise class or to a therapist who can create an individualized regimen, and then an individualized home-based regimen can be crafted. In addition to conventional exercise regimens, tai chi may be effective for knee OA. However, there is no strong evidence that patients with hand OA benefit from therapeutic exercise.

Adherence over the long term is the major challenge to an exercise prescription. In trials involving patients with knee OA, who are engaged in exercise treatment, from a third to over half of patients stopped exercising by 6 months. Less than 50% continued regular exercise at 1 year. T e strongest predictor of a patient's continued exercise is a previous personal history of successful exercise. Physicians should reinforce the exercise prescription at each clinic visit, help the patient recognize barriers to ongoing exercise, and identify convenient times for exercise to be done routinely. T e combination of exercise with calorie restriction and weight loss is especially effective in lessening pain.

Correction of Malalignment Malalignment in the frontal plane (varus-valgus) markedly increases the stress across the joint, which can lead to progression of disease and to pain and disability (Fig. 19-5). Correcting malalignment, either surgically or with bracing, may relieve pain in persons whose knees are malaligned. Malalignment develops over years as a consequence of gradual anatomic alterations of the joint and bone, and correcting it is often very challenging. One way is with a fitted brace, which takes an often varus osteoarthritic knee and straightens it by putting valgus stress across the knee. Unfortunately, many patients are unwilling to wear a realigning knee brace; in addition, in patients with obese legs, braces may slip with usage and lose their realigning effect. T ey are indicated for willing patients who can learn to put them on correctly and on whom they do not slip.

Other ways of correcting malalignment across the knee include the use of orthotics in footwear. Unfortunately, although they may have modest effects on knee alignment, trials have heretofore not demonstrated ef cacy of a lateral wedge orthotic versus placebo wedges.

Pain from the patellofemoral compartment of the knee can be caused by tilting of the patella or patellar malalignment with the patella riding laterally or medially in the femoral trochlear groove. Using a brace to realign the patella, or tape to pull the patella back into the trochlear sulcus or reduce its tilt, has been shown, when compared to placebo taping in clinical trials, to lessen patellofemoral pain. However, patients may find it dif cult to apply tape, and skin irritation from the tape is common. Commercial patellar braces may be a solution, but there is insuf cient evidence on their ef cacy to recommend them.

Although their effect on malalignment is questionable, neoprene sleeves pulled to cover the knee lessen pain and are easy to use and popular among patients. T e explanation for their therapeutic effect on pain is unclear.

In patients with knee OA, acupuncture produces modest pain relief compared to placebo needles and may be an adjunctive treatment.

PHARMACOTHERAPY Although nonpharmacologic approaches to therapy constitute its mainstay, pharmacotherapy serves an important adjunctive role in OA treatment. Available drugs are administered using oral, topical, and intraarticular routes.

Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and Cyclooxygenase-2 (COX-2) Inhibitors Acetaminophen (paracetamol) is the initial analgesic of choice for patients with OA in knees, hips, or hands. For some patients, it is adequate to control symptoms, in which case more toxic drugs such as NSAIDs can be avoided. Doses up to 1 g three times daily can be used **(Table 19-1)**.

NSAIDs are the most popular drugs to treat osteoarthritic pain. T ey can be administered either topically or orally. In clinical trials, oral NSAIDs produce ~30% greater improvement in pain than high-dose acetaminophen. Occasional patients treated with NSAIDs experience dramatic pain relief, whereas others experience little improvement. Initially, NSAIDs should be administered topically or taken orally on an "as needed" basis because side effects are less frequent with low intermittent doses. If occasional medication use is insuf ciently effective, then daily treatment may be indicated, with an anti-inflammatory dose selected (Table 19-1). Patients should be reminded to take low-dose aspirin and ibuprofen at different times to eliminate a drug interaction.

NSAIDs taken orally have substantial and frequent side effects, the most common of which is upper gastrointestinal toxicity, including dyspepsia, nausea, bloating, gastrointestinal bleeding, and ulcer disease. Some 30–40% of patients experience upper gastrointestinal (GI) side effects so severe as to require discontinuation of medication. To minimize the risk of nonsteroidal-related GI side effects, patients should not take two NSAIDs and should take medications after food;

TABLE 19-1

PHARMACOLOGIC TREATMENT FOR OSTEOARTHRITIS

TREATMENT	DOSAGE	COMMENTS
Acetaminophen	Up to 1 g tid	Prolongs half-life of warfarin. Make sure patient is not taking other treatments containing acetaminophen to avoid hepatic toxicity.
Oral NSAIDs and COX-2 inhibitors		Take with food. Increased risk of myocardial infarction and stroke for some NSAIDs and especially COX-2 inhibitors. High rates of gastrointestinal side effects, including ulcers and bleeding, occur. Patients at high risk for gastrointestinal side effects should also take either a proton pump inhibitor or misoprostol.[a] There is an increase in gastrointestinal side effects or bleeding when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency.
Naproxen	375–500 mg bid	
Salsalate	1500 mg bid	
Ibuprofen	600–800 mg 3–4 times a day	
Topical NSAIDs		Rub onto joint. Few systemic side effects. Skin irritation common.
Diclofenac Na 1% gel	4 g qid (for knees, hands)	
Opiates	Various	Common side effects include dizziness, sedation, nausea or vomiting, dry mouth, constipation, urinary retention, and pruritus. Respiratory and central nervous system depression can occur.
Capsaicin	0.025–0.075% cream 3–4 times a day	Can irritate mucous membranes.
Intraarticular injections		
Steroids		
Hyaluronans	Varies from 3–5 weekly injections depending on preparation	Mild to moderate pain at injection site. Controversy exists regarding efficacy.

[a]Patients at high risk include those with previous gastrointestinal events, persons ≥60 years, and persons taking glucocorticoids. Trials have shown the efficacy of proton pump inhibitors and misoprostol in the prevention of ulcers and bleeding. Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms.
Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.
Source: Adapted from DT Felson: N Engl J Med 354:841, 2006.

if risk is high, patients should take a gastroprotective agent, such as a proton pump inhibitor. Certain oral agents are safer to the stomach than others, including nonacetylated salicylates and nabumetone. Major NSAID-related GI side effects can occur in patients who do not complain of upper GI symptoms. In one study of patients hospitalized for GI bleeding, 81% had no premonitory symptoms.

Because of the increased rates of cardiovascular events associated with COX-2 inhibitors and with some conventional NSAIDs such as diclofenac, many of these drugs are not appropriate long-term treatment choices for older persons with OA, especially those at high risk of heart disease or stroke. The American Heart Association has identified rofecoxib and all other COX-2 inhibitors as putting patients at high risk, although low doses of celecoxib (≤200 mg/d) may not be associated with an elevation of risk. The only conventional NSAID that appears safe from a cardiovascular perspective is naproxen, but it does have GI toxicity.

There are other common side effects of NSAIDs, including the tendency to develop edema because of prostaglandin inhibition of afferent blood supply to glomeruli in the kidneys and, for similar reasons, a predilection toward reversible renal insufficiency. Blood pressure may increase modestly in some NSAID-treated patients. Oral NSAIDs should not be used in patients with stage IV or V renal disease and should be used with caution in those with stage III disease.

NSAIDs can be placed into a gel or topical solution with another chemical modality that enhances penetration of the skin barrier creating a topical NSAID. When absorbed through the skin, plasma concentrations are an order of magnitude lower than with the same amount of drug administered orally or parenterally. However, when these drugs are administered topically in proximity to a superficial joint (knees, hands, but not hips), the drug can be found in joint tissues such as the synovium and cartilage. Trial results have varied but generally have found that topical NSAIDs are slightly less efficacious than oral agents, but have far fewer GI and systemic side effects. Unfortunately, topical NSAIDs often cause local skin irritation where the medication is applied, inducing redness, burning, or itching in up to 40% of patients (see Table 19-1).

Intraarticular Injections: Glucocorticoids and Hyaluronic Acid Because synovial inflammation is likely to be a major cause of pain in patients with OA, local anti-inflammatory treatments administered intraarticularly may be effective in ameliorating pain, at least temporarily. Glucocorticoid injections provide such efficacy, but response is variable, with some patients having

little relief of pain whereas others experience pain relief lasting several months. Glucocorticoid injections are useful to get patients over acute flares of pain and may be especially indicated if the patient has coexistent OA and crystal deposition disease, especially from calcium pyrophosphate dihydrate crystals **(Chap. 20)**. There is no evidence that repeated glucocorticoid injections into the joint are dangerous.

Hyaluronic acid injections can be given for treatment of symptoms in knee and hip OA, but there is controversy as to whether they have efficacy versus placebo (Table 19-1).

Other Classes of Drugs and Nutraceuticals For patients with symptomatic knee or hip OA who have not had an adequate response to the treatments above and are either unwilling to undergo or are not candidates for total joint arthroplasty, opioid analgesics have shown modest efficacy and can be tried. Opioid management plans and patient selection are critical. Another option is the use of duloxetine, which has demonstrated modest efficacy in OA.

Recent guidelines recommend against the use of glucosamine or chondroitin for OA. Large publicly supported trials have failed to show that, compared with placebo, these compounds relieve pain in persons with disease.

Optimal nonsurgical therapy for OA is often achieved by trial and error, with each patient having idiosyncratic responses to specific treatments. When medical therapies have failed and the patient has an unacceptable reduction in their quality of life and ongoing pain and disability, then at least for knee and hip OA, total joint arthroplasty is indicated.

SURGERY For knee OA, several operations are available. Arthroscopic debridement and lavage have diminished in popularity after randomized trials evaluating this operation have showed that its efficacy is no greater than that of sham surgery or no treatment for relief of pain or disability. Even mechanical symptoms such as buckling, which are extremely common in patients with knee OA, do not respond to arthroscopic debridement. Although arthroscopic meniscectomy is indicated for acute meniscal tears in which symptoms such as locking and acute pain are clearly related temporally to a knee injury that produced the tear, recent trials show that doing a partial meniscectomy in persons with OA and a symptomatic meniscal tear does not relieve knee pain or improve function.

For patients with knee OA isolated to the medial compartment, operations to realign the knee to lessen medial loading can relieve pain. These include a high tibial osteotomy, in which the tibia is broken just below the tibial plateau and realigned so as to load the lateral, nondiseased compartment, or a unicompartmental replacement with realignment. Each surgery may provide the patient with years of pain relief before a total knee replacement is required.

Ultimately, when the patient with knee or hip OA has failed medical treatment modalities and remains in pain, with limitations of physical function that compromise the quality of life, the patient should be referred for total knee or hip arthroplasty. These are highly efficacious operations that relieve pain and improve function in the vast majority of patients, although rates of success are higher for hip than knee replacement. Currently failure rates for both are ~1% per year, although these rates are higher in obese patients. The chance of surgical success is greater in centers where at least 25 such operations are performed yearly or with surgeons who perform multiple operations annually. The timing of knee or hip replacement is critical. If the patient suffers for many years until their functional status has declined substantially, with considerable muscle weakness, postoperative functional status may not improve to a level achieved by others who underwent operation earlier in their disease course.

Cartilage Regeneration Chondrocyte transplantation has not been found to be efficacious in OA, perhaps because OA includes pathology of joint mechanics, which is not corrected by chondrocyte transplants. Similarly, abrasion arthroplasty (chondroplasty) has not been well studied for efficacy in OA, but it produces fibrocartilage in place of damaged hyaline cartilage. Both of these surgical attempts to regenerate and reconstitute articular cartilage may be more likely to be efficacious early in disease when joint malalignment and many of the other noncartilage abnormalities that characterize OA have not yet developed.

CHAPTER 20

GOUT AND OTHER CRYSTAL-ASSOCIATED ARTHROPATHIES

H. Ralph Schumacher ■ Lan X. Chen

The use of polarizing light microscopy during synovial fluid analysis in 1961 by McCarty and Hollander and the subsequent application of other crystallographic techniques, such as electron microscopy, energy-dispersive elemental analysis, and x-ray diffraction, have allowed investigators to identify the roles of different microcrystals, including monosodium urate (MSU), calcium pyrophosphate (CPP), calcium apatite (apatite), and calcium oxalate (CaOx), in inducing acute or chronic arthritis or periarthritis. The clinical events that result from deposition of MSU, CPP, apatite, and CaOx have many similarities but also have important differences. Because of often similar clinical presentations, the need to perform synovial fluid analysis to distinguish the type of crystal involved must be emphasized. Polarized light microscopy alone can identify most typical crystals; apatite, however, is an exception. Aspiration and analysis of effusions are also important to assess the possibility of infection. Apart from the identification of specific microcrystalline materials or organisms, synovial fluid characteristics in crystal-associated diseases are nonspecific, and synovial fluid can be inflammatory or noninflammatory. Without crystal identification, these diseases can be confused with rheumatoid or other types of arthritis. A list of possible musculoskeletal manifestations of crystal-associated arthritis is shown in **Table 20-1**.

TABLE 20-1

MUSCULOSKELETAL MANIFESTATIONS OF CRYSTAL-INDUCED ARTHRITIS	
Acute mono- or polyarthritis	Destructive arthropathies
Bursitis	Chronic inflammatory arthritis
Tendinitis	Spinal arthritis
Enthesitis	Peculiar type of osteoarthritis
Tophaceous deposits	Carpal tunnel syndrome

GOUT

Gout is a metabolic disease that most often affects middle-aged to elderly men and postmenopausal women. It results from an increased body pool of urate with hyperuricemia. It typically is characterized by episodic acute arthritis or chronic arthritis caused by deposition of MSU crystals in joints and connective tissue tophi and the risk for deposition in kidney interstitium or uric acid nephrolithiasis.

ACUTE AND CHRONIC ARTHRITIS

Acute arthritis is the most common early clinical manifestation of gout. Usually, only one joint is affected initially, but polyarticular acute gout can occur in subsequent episodes. The metatarsophalangeal joint of the first toe often is involved, but tarsal joints, ankles, and knees also are affected commonly. Especially in elderly patients or in advanced disease, finger joints may be involved. Inflamed Heberden's or Bouchard's nodes may be a first manifestation of gouty arthritis. The first episode of acute gouty arthritis frequently begins at night with dramatic joint pain and swelling. Joints rapidly become warm, red, and tender, with a clinical appearance that often mimics that of cellulitis. Early attacks tend to subside spontaneously within 3–10 days, and most patients have intervals of varying length with no residual symptoms until the next episode. Several events may precipitate acute gouty arthritis: dietary excess, trauma, surgery, excessive ethanol ingestion, hypouricemic therapy, and serious medical illnesses such as myocardial infarction and stroke.

After many acute mono- or oligoarticular attacks, a proportion of gouty patients may present with a chronic nonsymmetric synovitis, causing potential confusion with rheumatoid arthritis **(Chap. 6)**. Less commonly,

chronic gouty arthritis will be the only manifestation, and, more rarely, the disease will manifest only as periarticular tophaceous deposits in the absence of synovitis. Women represent only 5–20% of all patients with gout. Most women with gouty arthritis are postmenopausal and elderly, have osteoarthritis and arterial hypertension that causes mild renal insuf ciency, and usually are receiving diuretics. Premenopausal gout is rare. Kindreds of precocious gout in young females caused by decreased renal urate clearance and renal insuf ciency have been described.

Laboratory diagnosis

Even if the clinical appearance strongly suggests gout, the presumptive diagnosis ideally should be confirmed by needle aspiration of acutely or chronically involved joints or tophaceous deposits. Acute septic arthritis, several of the other crystalline-associated arthropathies, palindromic rheumatism, and psoriatic arthritis may present with similar clinical features. During acute gouty attacks, needle-shaped MSU crystals typically are seen both intracellularly and extracellularly **(Fig. 20-1)**. With compensated polarized light, these crystals are brightly birefringent with negative elongation. Synovial fluid leukocyte counts are elevated from 2000 to 60,000/μL. Effusions appear cloudy due to the increased numbers of leukocytes. Large amounts of crystals occasionally produce a thick pasty or chalky joint fluid. Bacterial infection can coexist with urate crystals in synovial fluid; if there is any suspicion of septic arthritis, joint fluid must be cultured.

MSU crystals also can often be demonstrated in the first metatarsophalangeal joint and in knees not acutely involved with gout. Arthrocentesis of these joints is a useful technique to establish the diagnosis of gout between attacks.

Serum uric acid levels can be normal or low at the time of an acute attack, as inflammatory cytokines can be uricosuric and effective initiation of hypouricemic therapy can precipitate attacks. T is limits the value of serum uric acid determinations for the diagnosis of gout. Nevertheless, serum urate levels are almost always elevated at some time and are important to use to follow the course of hypouricemic therapy. A 24-h urine collection for uric acid can, in some cases, be useful in assessing the risk of stones, elucidating overproduction or underexcretion of uric acid, and deciding whether it may be appropriate to use a uricosuric therapy. Excretion of >800 mg of uric acid per 24 h on a regular diet suggests that causes of overproduction of purine should be considered. Urinalysis, serum creatinine, hemoglobin, white blood cell (WBC) count, liver function tests, and serum lipids should be obtained because of possible pathologic sequelae of gout and other associated diseases requiring treatment and as baselines because of possible adverse effects of gout treatment.

Radiographic features

Cystic changes, well-defined erosions with sclerotic margins (often with overhanging bony edges), and soft tissue masses are characteristic radiographic features of advanced chronic tophaceous gout. Ultrasound may aid earlier diagnosis by showing a double contour sign overlying the articular cartilage. Dual-energy computed tomography (CT) can show specific features establishing the presence of urate crystals.

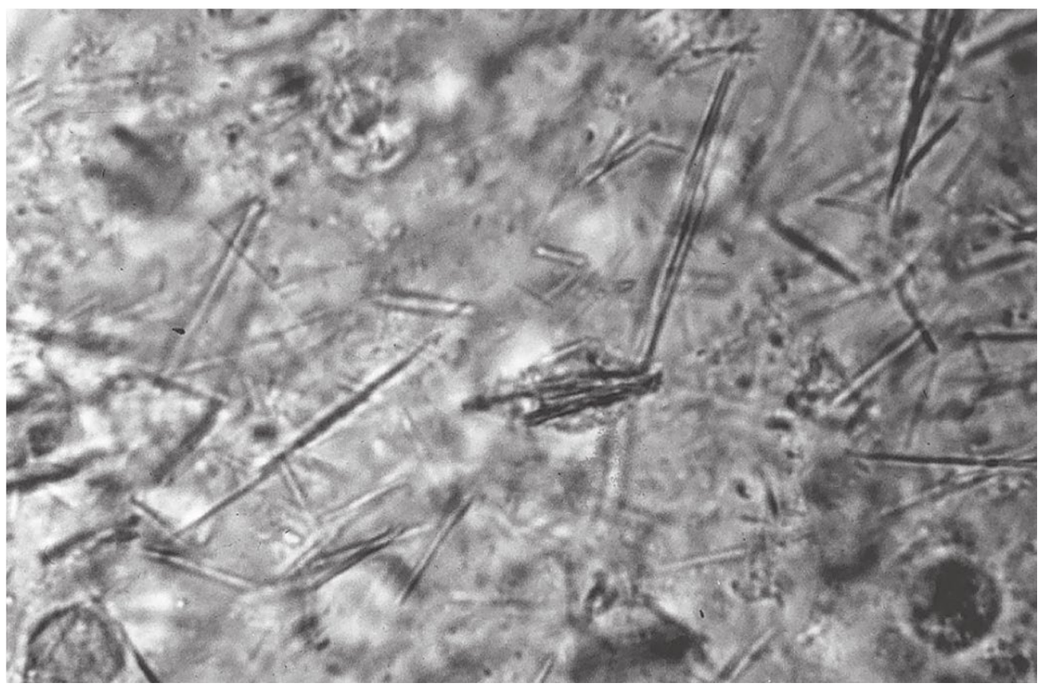


FIGURE 20-1
Extracellular and intracellular monosodium urate crystals, as seen in a fresh preparation of synovial fluid, illustrate needle- and rod-shaped crystals. These crystals are strongly negative birefringent crystals under compensated polarized light microscopy; 400×.

TREATMENT Gout

ACUTE GOUTY ARTHRITIS T e mainstay of treatment during an acute attack is the administration of anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or glucocorticoids. NSAIDs are used most often in individuals without complicating comorbid conditions. Both colchicine and NSAIDs may be poorly tolerated and dangerous in the elderly and in the presence of renal insuf ciency and gastrointestinal disorders. Ice pack applications and rest of the involved joints can be helpful. Colchicine given orally is a traditional and effective treatment if used early in an attack. Useful regimens are one 0.6-mg tablet given every 8 h with subsequent tapering or 1.2 mg followed by 0.6 mg in 1 h with subsequent day dosing depending on response. T is is generally better tolerated than the formerly advised higher dose regimens. T e drug must be at least temporarily discontinued promptly at the first sign of loose stools, and symptomatic treatment must be given for the diarrhea.

Intravenous colchicine has been taken off the market. NSAIDs given in full anti-inflammatory doses are effective in □90% of patients, and the resolution of signs and symptoms usually occurs in 5–8 days. T e most effective drugs are any of those with a short half-life and include indomethacin, 25–50 mg tid; naproxen, 500 mg bid; ibuprofen, 800 mg tid; diclofenac, 50 mg tid; and celecoxib 800 mg followed by 400 mg 12 h later, then 400 mg bid.

Glucocorticoids given IM or orally, for example, prednisone, 30–50 mg/d as the initial dose and gradually tapered with the resolution of the attack, can be effective in polyarticular gout. For a single joint or a few involved joints, intraarticular triamcinolone acetonide, 20–40 mg, or methylprednisolone, 25–50 mg, have been effective and well tolerated. Based on recent evidence on the essential role of the inflammasome and interleukin 1β (IL-1β) in acute gout, anakinra has been used, and other inhibitors of IL-1β, including canakinumab and rilonacept, are under investigation.

HYPOURICEMIC THERAPY Ultimate control of gout requires correction of the basic underlying defect: the hyperuricemia. Attempts to normalize serum uric acid to <300–360 μmol/L (5.0–6.0 mg/dL) to prevent recurrent gouty attacks and eliminate tophaceous deposits are critical and entail a commitment to hypouricemic regimens and medications that generally are required for life. Hypouricemic drug therapy should be considered when, as in most patients, the hyperuricemia cannot be corrected by simple means (control of body weight, low-purine diet, increase in liquid intake, limitation of ethanol use, decreased use of fructose-containing foods and beverages, and avoidance of diuretics). T e decision to initiate hypouricemic therapy usually is made taking into consideration the number of acute attacks (urate lowering may be cost-effective after two attacks), serum uric acid levels (progression is more rapid in patients with serum uric acid >535 μmol/L [>9.0 mg/dL]), the patient's willingness to commit to lifelong therapy, or the presence of uric acid stones. Urate-lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis. Uricosuric agents such as probenecid can be used in patients with good renal function who underexcrete uric acid, with <600 mg in a 24-h urine sample. Urine volume should be maintained by ingestion of 1500 mL of water every day. Probenecid can be started at a dose of 250 mg twice daily and increased gradually as needed up to 3 g per day to achieve and maintain a serum uric acid level of less than 6 mg/dL. Probenecid is generally not effective in patients with serum creatinine levels >177 μmol/L (2 mg/dL). T ese patients may require allopurinol or benzbromarone (not available in the United States). Benzbromarone is another uricosuric drug that is more effective in patients with chronic kidney disease. Some agents used to treat common comorbidities, including losartan, fenofibrate, and amlodipine, have some mild uricosuric effects.

T e xanthine oxidase inhibitor allopurinol is by far the most commonly used hypouricemic agent and is the best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease. It can be given in a single morning dose, usually 100 mg initially and increasing up to 800 mg if needed. In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration; for example, with a creatinine clearance of 10 mL/min, one generally would use 100 mg every other day. Doses can be increased gradually to reach the target urate level of less than 6 mg/dL. Toxicity of allopurinol has been recognized increasingly in patients who use thiazide diuretics, in patients allergic to penicillin and ampicillin, and in Asians expressing HLA-B*5801. T e most serious side effects include life-threatening toxic epidermal necrolysis, systemic vasculitis, bone marrow suppression, granulomatous hepatitis, and renal failure. Patients with mild cutaneous reactions to allopurinol can reconsider the use of a uricosuric agent, undergo an attempt at desensitization to allopurinol, or take febuxostat, a new, chemically unrelated specific xanthine oxidase inhibitor. Febuxostat is approved in the United States at 40 or 80 mg once a day and does not require dose adjustment in mild to moderate renal disease. Pegloticase is a pegylated uricase, now available for patients who do not tolerate or fail full doses of other treatments. It is given intravenously usually at 8 mg every 2 weeks and can dramatically lower serum uric acid in up to 50% of such patients. Pegloticase can be associated with severe infusions reactions that occur with higher frequency when the uric acid level increases to above 6 mg/dL during treatment. New uricosurics are also undergoing investigation.

Urate-lowering drugs are generally not initiated during acute attacks but after the patient is stable and low-dose colchicine has been initiated to decrease the risk of the flares that often occur with urate lowering. Colchicine anti-inflammatory prophylaxis in doses of 0.6 mg one to two times daily should be given along with the hypouricemic therapy until the patient is normouricemic and without gouty attacks for 6 months or as long as tophi are present. Colchicine should not be used in dialysis patients and is given in lower doses in patients with renal disease or with P glycoprotein or CYP3A4 inhibitors such as clarithromycin that can increase toxicity of colchicine.

CALCIUM PYROPHOSPHATE DEPOSITION (CPPD) DISEASE

PATHOGENESIS

T e deposition of CPP crystals in articular tissues is most common in the elderly, occurring in 10–15% of persons age 65–75 years and 30–50% of those >85 years. In most cases, this process is asymptomatic and the cause of CPPD is uncertain. Because >80% of patients are >60 years and 70% have preexisting joint damage from other conditions, it is likely that biochemical changes in aging or diseased cartilage favor crystal nucleation. In patients with CPPD arthritis, there

is increased production of inorganic pyrophosphate and decreased levels of pyrophosphatases in cartilage extracts. Mutations in the ANKH gene, as described in both familial and sporadic cases, can increase elaboration and extracellular transport of pyrophosphate. T e increase in pyrophosphate production appears to be related to enhanced activity of ATP pyrophosphohydrolase and 5′-nucleotidase, which catalyze the reaction of ATP to adenosine and pyrophosphate. T is pyrophosphate could combine with calcium to form CPP crystals in matrix vesicles or on collagen fibers. T ere are decreased levels of cartilage glycosaminoglycans that normally inhibit and regulate crystal nucleation. High activities of transglutaminase enzymes also may contribute to the deposition of CPP crystals.

Release of CPP crystals into the joint space is followed by the phagocytosis of those crystals by monocyte-macrophages and neutrophils, which respond by releasing chemotactic and inflammatory substances and, as with MSU crystals, activating the inflammasome.

A minority of patients with CPPD arthropathy have metabolic abnormalities or hereditary CPP disease **(Table 20-2)**. T ese associations suggest that a variety of different metabolic products may enhance CPP crystal deposition either by directly altering cartilage or by inhibiting inorganic pyrophosphatases. Included among these conditions are hyperparathyroidism, hemochromatosis, hypophosphatasia, hypomagnesemia, and possibly myxedema. T e presence of CPPD arthritis in individuals <50 years old should lead to consideration of these metabolic disorders (Table 20-2) and inherited forms of disease, including those identified in a variety of ethnic groups. Genomic DNA studies performed on different kindreds have shown a possible location of genetic defects on chromosome 8q or on chromosome 5p in a region that expresses the gene of the membrane pyrophosphate channel (ANKH gene). As noted above, mutations described in the ANKH gene in kindreds with CPPD arthritis can increase extracellular pyrophosphate and induce CPP crystal formation.

TABLE 20-2

CONDITIONS ASSOCIATED WITH CALCIUM PYROPHOSPHATE CRYSTAL DEPOSITION DISEASE
Aging
Disease-associated
Primary hyperparathyroidism
Hemochromatosis
Hypophosphatasia
Hypomagnesemia
Chronic gout
Postmeniscectomy
Gitelman's syndrome
Epiphyseal dysplasias

Investigation of younger patients with CPPD should include inquiry for evidence of familial aggregation and evaluation of serum calcium, phosphorus, alkaline phosphatase, magnesium, iron, and transferrin.

CLINICAL MANIFESTATIONS

CPPD arthropathy may be asymptomatic, acute, subacute, or chronic or may cause acute synovitis superimposed on chronically involved joints. Acute CPPD arthritis originally was termed pseudogout by McCarty and co-workers because of its striking similarity to gout. Other clinical manifestations of CPPD include (1) association with or enhancement of peculiar forms of osteoarthritis; (2) induction of severe destructive disease that may radiographically mimic neuropathic arthritis; (3) production of chronic symmetric synovitis that is clinically similar to rheumatoid arthritis; (4) intervertebral disk and ligament calcification with restriction of spine mobility, the crowned dens syndrome, or spinal stenosis (most commonly seen in the elderly); and (5) rarely periarticular tophus-like nodules.

T e knee is the joint most frequently affected in CPPD arthropathy. Other sites include the wrist, shoulder, ankle, elbow, and hands. T e temporomandibular joint may be involved. Clinical and radiographic evidence indicates that CPPD deposition is polyarticular in at least two-thirds of patients. When the clinical picture resembles that of slowly progressive osteoarthritis, diagnosis may be dif cult. Joint distribution may provide important clues suggesting CPPD disease. For example, primary osteoarthritis less often involves metacarpophalangeal, wrist, elbow, shoulder, or ankle joints. If radiographs or ultrasound reveal punctate and/or linear radiodense deposits within fibrocartilaginous joint menisci or articular hyaline cartilage (chondrocalcinosis), the diagnostic likelihood of CPPD disease is further increased. Def nitive diagnosis requires demonstration of typical rhomboid or rodlike crystals (generally weakly positively birefringent or nonbirefringent with polarized light) in synovial fluid or articular tissue **(Fig. 20-2)**. In the absence of joint effusion or indications to obtain a synovial biopsy, chondrocalcinosis is presumptive of CPPD. One exception is chondrocalcinosis due to CaOx in some patients with chronic renal failure.

Acute attacks of CPPD arthritis may be precipitated by trauma. Rapid diminution of serum calcium concentration, as may occur in severe medical illness or after surgery (especially parathyroidectomy), can also lead to attacks.

In as many as 50% of cases, episodes of CPPD-induced inflammation are associated with low-grade fever and, on occasion, temperatures as high as 40°C (104°F). In such cases, synovial fluid analysis with microbial cultures is essential to rule out the possibility of infection. In fact, infection in a joint with any

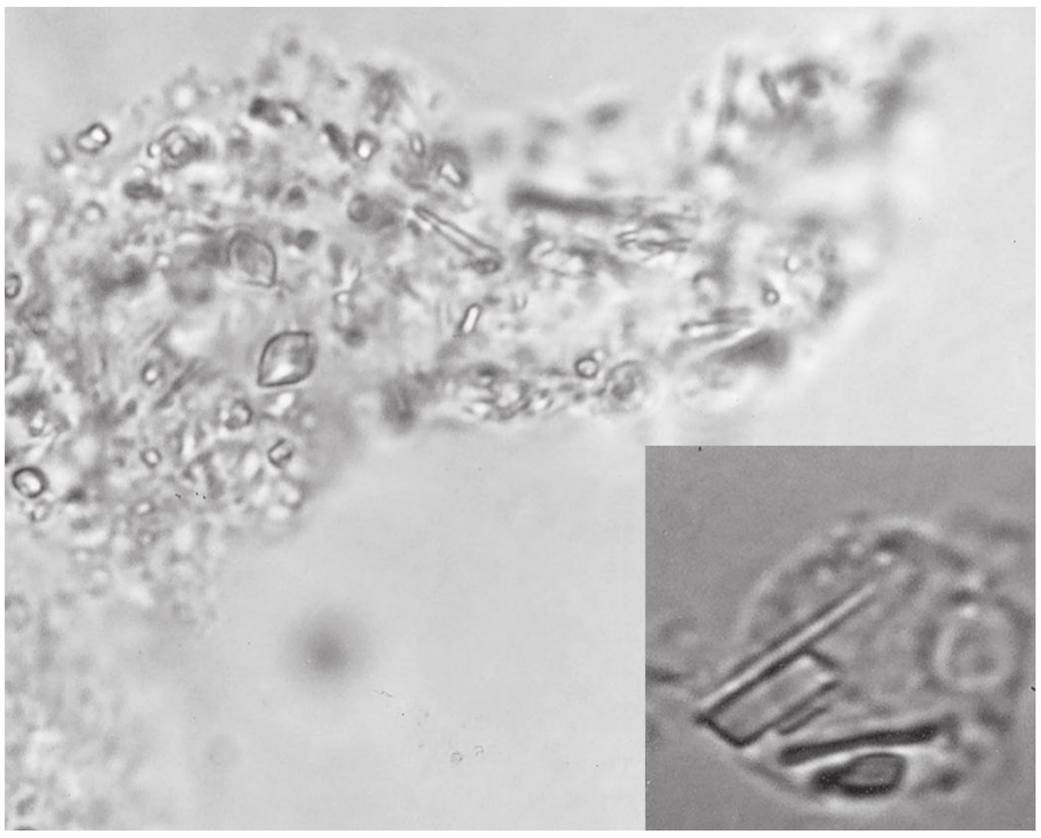


FIGURE 20-2
Intracellular and extracellular calcium pyrophosphate (CPP) crystals, as seen in a fresh preparation of synovial fluid, illustrate rectangular, rod-shaped, and rhomboid crystals that are weakly positively or nonbirefringent crystals (compensated polarized light microscopy; 400×).

microcrystalline deposition process can lead to crystal shedding and subsequent synovitis from both crystals and microorganisms. T e leukocyte count in synovial fluid in acute CPPD can range from several thousand cells to 100,000 cells/μL, with the mean being about 24,000 cells/μL and the predominant cell being the neutrophil. CPP crystals may be seen inside tissue fragments and fibrin clots and in neutrophils (Fig. 20-2). CPP crystals may coexist with MSU and apatite in some cases.

TREATMENT CPPD Disease

Untreated acute attacks may last a few days to as long as a month. Treatment by rest, joint aspiration, and NSAIDs or by intraarticular glucocorticoid injection may result in more rapid return to prior status. For patients with frequent recurrent attacks, daily prophylactic treatment with low doses of colchicine may be helpful in decreasing the frequency of the attacks. Severe polyarticular attacks usually require short courses of glucocorticoids or, as recently reported, an IL-1β antagonist, anakinra. Unfortunately, there is no effective way to remove CPP deposits from cartilage and synovium. Uncontrolled studies suggest that the administration of NSAIDS (with a gastric protective agent if required), hydroxychloroquine, or even methotrexate may be helpful in controlling persistent synovitis. Patients with progressive destructive large-joint arthropathy may require joint replacement.

CALCIUM APATITE DEPOSITION DISEASE

PATHOGENESIS

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation of basic calcium phosphates, largely carbonate substituted apatite, can occur in areas of tissue damage (dystrophic calcification), hypercalcemic or hyperparathyroid states (metastatic calcification), and certain conditions of unknown cause **(Table 20-3)**. In chronic renal failure, hyperphosphatemia can contribute to extensive apatite deposition both in and around joints. Familial aggregation is rarely seen; no association with ANKH mutations has been described thus far. Apatite crystals are deposited primarily on matrix vessels. Incompletely understood alterations in matrix proteoglycans, phosphatases, hormones, and cytokines probably can influence crystal formation.

Apatite aggregates are commonly present in synovial fluid in an extremely destructive chronic arthropathy of the elderly that occurs most often in the shoulders (Milwaukee shoulder) and in a similar process in hips, knees, and erosive osteoarthritis of fingers. Joint destruction is associated with damage to cartilage and supporting structures, leading to instability and deformity. Progression tends to be indolent. Symptoms range from minimal to severe pain and disability that may lead to joint replacement surgery. Whether severely affected patients represent an extreme synovial tissue response to the apatite crystals that are so common in osteoarthritis

TABLE 20-3

CONDITIONS ASSOCIATED WITH APATITE DEPOSITION DISEASE
Aging
Osteoarthritis
Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder)
Destructive arthropathy
Tendinitis, bursitis
Tumoral calcinosis (sporadic cases)
Disease-associated
Hyperparathyroidism
Milk-alkali syndrome
Renal failure/long-term dialysis
Connective tissue diseases (e.g., systemic sclerosis, dermatomyositis, SLE)
Heterotopic calcif cation after neurologic catastrophes (e.g., stroke, spinal cord injury)
Heredity
Bursitis, arthritis
Tumoral calcinosis
Fibrodysplasia ossif cans progressiva

Abbreviation: SLE, systemic lupus erythematosus.

is uncertain. Synovial lining cell or fibroblast cultures exposed to apatite (or CPP) crystals can undergo mitosis and markedly increase the release of prostaglandin E_2, various cytokines, and also collagenases and neutral proteases, underscoring the destructive potential of abnormally stimulated synovial lining cells.

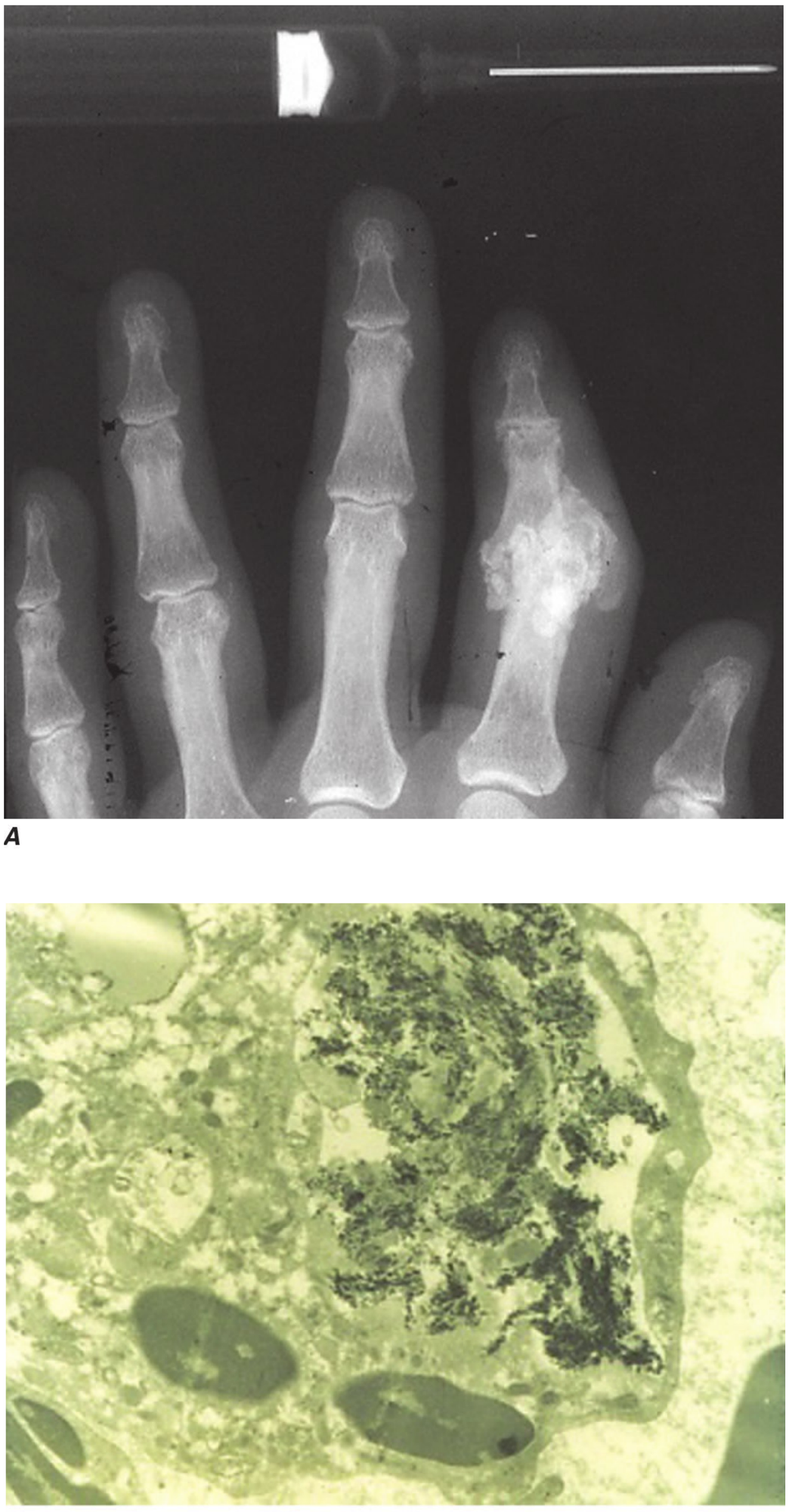
CLINICAL MANIFESTATIONS

Periarticular or articular deposits may occur and may be associated with acute reversible inflammation and/or chronic damage to the joint capsule, tendons, bursa, or articular surfaces. T e most common sites of apatite deposition include bursae and tendons in and/or around the knees, shoulders, hips, and fingers. Clinical manifestations include asymptomatic radiographic abnormalities, acute synovitis, bursitis, tendinitis, and chronic destructive arthropathy. Although the true incidence of apatite arthritis is not known, 30–50% of patients with osteoarthritis have apatite microcrystals in their synovial fluid. Such crystals frequently can be identified in clinically stable osteoarthritic joints, but they are more likely to come to attention in persons experiencing acute or subacute worsening of joint pain and swelling. T e synovial fluid leukocyte count in apatite arthritis is usually low (<2000/μL) despite dramatic symptoms, with predominance of mononuclear cells.

DIAGNOSIS

Intra- and/or periarticular calcifications with or without erosive, destructive, or hypertrophic changes may be seen on radiographs **(Fig. 20-3)**. T ey should be distinguished from the linear calcifications typical of CPPD.

Definitive diagnosis of apatite arthropathy, also called basic calcium phosphate disease, depends on identification of crystals from synovial fluid or tissue (Fig. 20-3). Individual crystals are very small and can be seen only by electron microscopy. Clumps of crystals may appear as 1- to 20-μm shiny intra- or extracellular nonbirefringent globules or aggregates that stain purplish with Wright's stain and bright red with alizarin red S. Tetracycline binding and other investigative techniques are under consideration as labeling alternatives. Absolute identification depends on electron microscopy with energy-dispersive elemental analysis, x-ray diffraction, infrared spectroscopy, or Raman microspectroscopy, but these techniques usually are not required in clinical diagnosis.



A

B

FIGURE 20-3

A. Radiograph showing calcif cation due to apatite crystals surrounding an eroded joint. B. An electron micrograph demonstrates dark needle-shaped apatite crystals within a vacuole of a synovial fluid mononuclear cell (30,000×).

TREATMENT Calcium Apatite Deposition Disease

Treatment of apatite arthritis or periarthritis is nonspecific. Acute attacks of bursitis or synovitis may be self-limiting, resolving in days to several weeks. Aspiration of effusions and the use of either NSAIDs or oral colchicine for 2 weeks or intra- or periarticular injection of a depot glucocorticoid appear to shorten the duration and intensity of symptoms. Local injection of disodium ethylenediaminetetraacetic acid (EDTA) and SC anakinra have been suggested as effective in single studies of acute calcific tendinitis at the shoulder. Other reports have described that IV gamma globulin, rituximab, calcium channel blockers, or bisphosphonates may help diffuse calcinosis. Periarticular apatite deposits may be resorbed with resolution of attacks. Agents to lower

serum phosphate levels may lead to resorption of deposits in renal failure patients receiving hemodialysis. In patients with underlying severe destructive articular changes, response to medical therapy is usually less rewarding.

CaOx DEPOSITION DISEASE

PATHOGENESIS

Primary oxalosis is a rare hereditary metabolic disorder. Enhanced production of oxalic acid may result from at least two different enzyme defects, leading to hyperoxalemia and deposition of CaOx crystals in tissues. Nephrocalcinosis and renal failure are typical results. Acute and/or chronic CaOx arthritis, periarthritis, and bone disease may complicate primary oxalosis during later years of illness.

Secondary oxalosis is more common than the primary disorder. In chronic renal disease, calcium oxalate deposits have long been recognized in visceral organs, blood vessels, bones, and cartilage and are now known to be one of the causes of arthritis in chronic renal failure. T us far, reported patients have been dependent on long-term hemodialysis or peritoneal dialysis, and many had received ascorbic acid supplements. Ascorbic acid is metabolized to oxalate, which is inadequately cleared in uremia and by dialysis. Such supplements and foods high in oxalate content usually are avoided in dialysis programs because of the risk of enhancing hyperoxalosis and its sequelae.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

CaOx aggregates can be found in bone, articular cartilage, synovium, and periarticular tissues. From these sites, crystals may be shed, causing acute synovitis. Persistent aggregates of CaOx can, like apatite and CPP, stimulate synovial cell proliferation and enzyme release, resulting in progressive articular destruction. Deposits have been documented in fingers, wrists, elbows, knees, ankles, and feet.

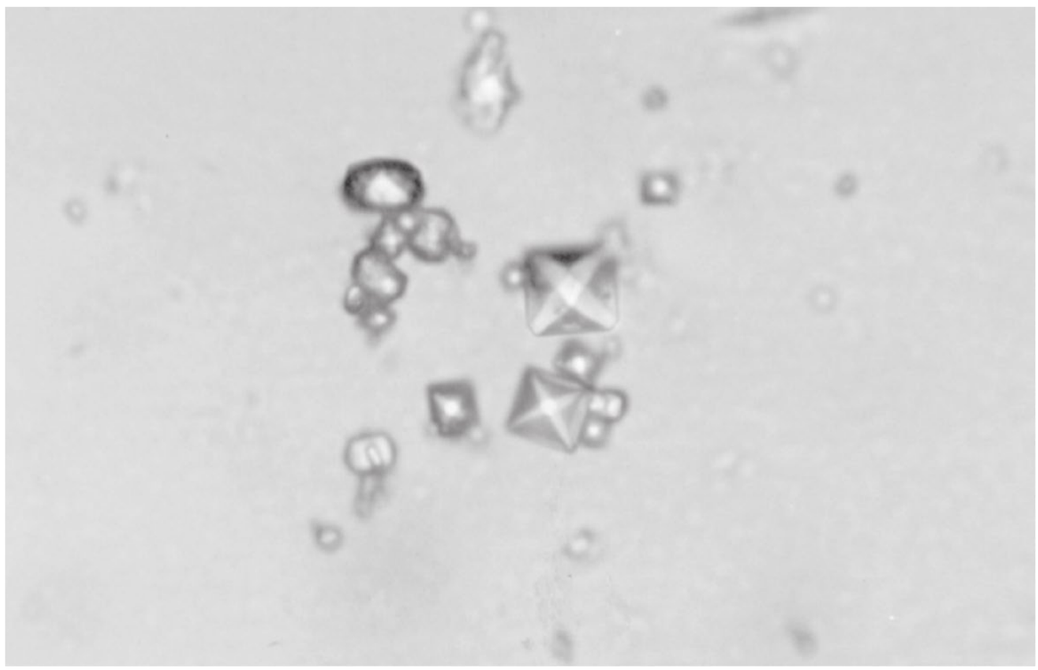


FIGURE 20-4
Bipyramidal and small polymorphic calcium oxalate crystals from synovial fluid are a classic finding in calcium oxalate arthropathy (ordinary light microscopy; 400×).

Clinical features of acute CaOx arthritis may not be distinguishable from those due to urate, CPP, or apatite. Radiographs may reveal chondrocalcinosis or soft tissue calcifications. CaOx-induced synovial effusions are usually noninflammatory, with <2000 leukocytes/μL, or mildly inflammatory. Neutrophils or mononuclear cells can predominate. CaOx crystals have a variable shape and variable birefringence to polarized light. T e most easily recognized forms are bipyramidal, have strong birefringence **(Fig. 20-4)**, and stain with alizarin red S.

TREATMENT Calcium Oxalate Deposition Disease

Treatment of CaOx arthropathy with NSAIDs, colchicine, intraarticular glucocorticoids, and/or an increased frequency of dialysis has produced only slight improvement. In primary oxalosis, liver transplantation has induced a significant reduction in crystal deposits.

Acknowledgment
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CHAPTER 21

INFECTIOUS ARTHRITIS

Lawrence C. Madoff

Although Staphylococcus aureus, Neisseria gonorrhoeae, and other bacteria are the most common causes of infectious arthritis, various mycobacteria, spirochetes, fungi, and viruses also infect joints **(Table 21-1)**. Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures.

Acute bacterial infection typically involves a single joint or a few joints. Subacute or chronic monarthritis or oligoarthritis suggests mycobacterial or fungal infection; episodic inflammation is seen in syphilis, Lyme disease, and the reactive arthritis that follows enteric infections and chlamydial urethritis. Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute hepatitis B. Bacteria and viruses occasionally infect multiple joints, the former most commonly in persons with rheumatoid arthritis.

APPROACH TO THE PATIENT: Infectious Arthritis

Aspiration of synovial fluid—an essential element in the evaluation of potentially infected joints—can be performed without difficulty in most cases by the insertion of a large-bore needle into the site of maximal fluctuance or tenderness or by the route of easiest access. Ultrasonography or fluoroscopy may be used to guide aspiration of difficult-to-localize effusions of the hip and, occasionally, the shoulder and other joints. Normal synovial fluid contains <180 cells (predominantly mononuclear cells) per microliter. Synovial cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% neutrophils, are characteristic of acute bacterial infections. Crystal-induced, rheumatoid, and other noninfectious inflammatory arthritides usually are associated with <30,000–50,000 cells/μL; cell counts of 10,000–30,000/μL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections. Definitive diagnosis of an infectious process relies on identification of the pathogen in stained smears of synovial fluid, isolation of the pathogen from cultures of synovial fluid and blood, or detection of microbial nucleic acids and proteins by nucleic acid amplification (NAA)–based assays and immunologic techniques.

ACUTE BACTERIAL ARTHRITIS

PATHOGENESIS

Bacteria enter the joint from the bloodstream; from a contiguous site of infection in bone or sof tissue; or by direct inoculation during surgery, injection, animal or human bite, or trauma. In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium. Neutrophils and bacteria enter the joint space; later, bacteria adhere to articular cartilage. Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells. Histologic studies reveal bacteria lining the synovium and cartilage as well as abscesses extending into the synovium, cartilage, and—in severe cases—subchondral bone. Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops. Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in S. aureus

TABLE 21-1

DIFFERENTIAL DIAGNOSIS OF ARTHRITIS SYNDROMES

ACUTE MONARTICULAR ARTHRITIS	CHRONIC MONARTICULAR ARTHRITIS	POLYARTICULAR ARTHRITIS
Staphylococcus aureus	Mycobacterium tuberculosis	Neisseria meningitidis
Streptococcus pneumoniae	Nontuberculous mycobacteria	N. gonorrhoeae
β-Hemolytic streptococci	Borrelia burgdorferi	Nongonococcal bacterial arthritis
Gram-negative bacilli	Treponema pallidum	Bacterial endocarditis
Neisseria gonorrhoeae	Candida spp.	Candida spp.
Candida spp.	Sporothrix schenckii	Poncet's disease (tuberculous rheumatism)
Crystal-induced arthritis	Coccidioides immitis	Hepatitis B virus
Fracture	Blastomyces dermatitidis	Parvovirus B19
Hemarthrosis	Aspergillus spp.	HIV
Foreign body	Cryptococcus neoformans	Human T-lymphotropic virus type I
Osteoarthritis	Nocardia spp.	Rubella virus
Ischemic necrosis	Brucella spp.	Arthropod-borne viruses
Monarticular rheumatoid arthritis	Legg-Calvé-Perthes disease	Sickle cell disease flare
	Osteoarthritis	Reactive arthritis
		Serum sickness
		Acute rheumatic fever
		Inflammatory bowel disease
		Systemic lupus erythematosus
		Rheumatoid arthritis/Still's disease
		Other vasculitides
		Sarcoidosis

that permit adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

MICROBIOLOGY

The hematogenous route of infection is the most common route in all age groups, and nearly every bacterial pathogen is capable of causing septic arthritis. In infants, group B streptococci, gram-negative enteric bacilli, and S. aureus are the most common pathogens. Since the advent of the Haemophilus influenzae vaccine, the predominant causes among children <5 years of age have been S. aureus, Streptococcus pyogenes (group A Streptococcus), and (in some centers) Kingella kingae. Among young adults and adolescents, N. gonorrhoeae is the most commonly implicated organism. S. aureus accounts for most nongonococcal isolates in adults of all ages; gram-negative bacilli, pneumococci, and β-hemolytic streptococci—particularly groups A and B but also groups C, G, and F—are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses.

Infections after surgical procedures or penetrating injuries are due most often to S. aureus and occasionally to other gram-positive bacteria or gram-negative bacilli. Infections with coagulase-negative staphylococci are unusual except after the implantation of prosthetic joints or arthroscopy. Anaerobic organisms, often in association with aerobic or facultative bacteria, are found after human bites and when decubitus ulcers or intraabdominal abscesses spread into adjacent joints. Polymicrobial infections complicate traumatic injuries with extensive contamination. Bites and scratches from cats and other animals may introduce Pasteurella multocida or Bartonella henselae into joints either directly or hematogenously, and bites from humans may introduce Eikenella corrodens or other components of the oral flora. Penetration of a sharp object through a shoe is associated with Pseudomonas aeruginosa arthritis in the foot.

NONGONOCOCCAL BACTERIAL ARTHRITIS

Epidemiology

Although hematogenous infections with virulent organisms such as S. aureus, H. influenzae, and pyogenic streptococci occur in healthy persons, there is an underlying host predisposition in many cases of septic arthritis. Patients with rheumatoid arthritis have the highest incidence of infective arthritis (most often secondary to S. aureus) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints. Diabetes mellitus, glucocorticoid therapy, hemodialysis, and malignancy all carry an increased risk of infection with S. aureus and gram-negative bacilli. Tumor necrosis factor inhibitors (e.g., etanercept, infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic

bacterial infections and could be associated with septic arthritis in this population. Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies. Pneumococci, Salmonella species, and H. influenzae cause septic arthritis in persons infected with HIV. Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly. IV drug users acquire staphylococcal and streptococcal infections from their own flora and acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

Clinical manifestations

Some 90% of patients present with involvement of a single joint—most commonly the knee; less frequently the hip; and still less often the shoulder, wrist, or elbow. Small joints of the hands and feet are more likely to be affected after direct inoculation or a bite. Among IV drug users, infections of the spine, sacroiliac joints, and sternoclavicular joints **(Fig. 21-1)** are more common than infections of the appendicular skeleton. Polyarticular infection is most common among patients with rheumatoid arthritis and may resemble a flare of the underlying disease.



FIGURE 21-1
Acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with a new onset of fever and lower neck pain. He had no history of IV drug use or previous catheter placement. Jaundice and a painful swollen area over his left sternoclavicular joint were evident on physical examination. Cultures of blood drawn at admission grew group B Streptococcus. The patient recovered after treatment with IV penicillin. (Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.)

The usual presentation consists of moderate to severe pain that is uniform around the joint, effusion, muscle spasm, and decreased range of motion. Fever in the range of 38.3–38.9°C (101–102°F) and sometimes higher is common but may not be present, especially in persons with rheumatoid arthritis, renal or hepatic insufficiency, or conditions requiring immunosuppressive therapy. The inflamed, swollen joint is usually evident on examination except in the case of a deeply situated joint such as the hip, shoulder, or sacroiliac joint. Cellulitis, bursitis, and acute osteomyelitis, which may produce a similar clinical picture, should be distinguished from septic arthritis by their greater range of motion and less-than-circumferential swelling. A focus of extraarticular infection, such as a boil or pneumonia, should be sought. Peripheral-blood leukocytosis with a left shift and elevation of the erythrocyte sedimentation rate or C-reactive protein level are common.

Plain radiographs show evidence of soft-tissue swelling, joint-space widening, and displacement of tissue planes by the distended capsule. Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis. Ultrasound is useful for detecting effusions in the hip, and CT or MRI can demonstrate infections of the sacroiliac joint, the sternoclavicular joint, and the spine very well.

Laboratory findings

Specimens of peripheral blood and synovial fluid should be obtained before antibiotics are administered. Blood cultures are positive in up to 50–70% of S. aureus infections but are less frequently positive in infections due to other organisms. The synovial fluid is turbid, serosanguineous, or frankly purulent. Gram-stained smears confirm the presence of large numbers of neutrophils. Levels of total protein and lactate dehydrogenase in synovial fluid are elevated, and the glucose level is depressed; however, these findings are not specific for infection, and measurement of these levels is not necessary for diagnosis. The synovial fluid should be examined for crystals, because gout and pseudogout can resemble septic arthritis clinically, and infection and crystal-induced disease occasionally occur together. Organisms are seen on synovial fluid smears in nearly three-quarters of infections with S. aureus and streptococci and in 30–50% of infections due to gram-negative and other bacteria. Cultures of synovial fluid are positive in >90% of cases. Inoculation of synovial fluid into bottles containing liquid media for blood cultures increases the yield of a culture, especially if the pathogen is a fastidious organism or the patient is taking an antibiotic. NAA-based assays for bacterial DNA, when available, can be useful for the diagnosis of partially treated or culture-negative bacterial arthritis.

TREATMENT Nongonococcal Bacterial Arthritis

Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity. Once samples of blood and synovial fluid have been obtained for culture, empirical antibiotics should be given that are directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient's age and risk factors. Initial therapy should consist of IV administration of bactericidal agents; direct instillation of antibiotics into the joint is not necessary to achieve adequate levels in synovial fluid and tissue. An IV third-generation cephalosporin such as cefotaxime (1 g every 8 h) or ceftriaxone (1–2 g every 24 h) provides adequate empirical coverage for most community-acquired infections in adults when smears show no organisms. IV vancomycin (1 g every 12 h) is used if there are gram-positive cocci on the smear. If methicillin-resistant S. aureus is an unlikely pathogen (e.g., when it is not widespread in the community), either oxacillin or nafcillin (2 g every 4 h) should be given. In addition, an aminoglycoside or third-generation cephalosporin should be given to IV drug users and to other patients in whom P. aeruginosa may be the responsible agent.

Definitive therapy is based on the identity and antibiotic susceptibility of the bacteria isolated in culture. Infections due to staphylococci are treated with oxacillin, nafcillin, or vancomycin for 4 weeks. Pneumococcal and streptococcal infections due to penicillin-susceptible organisms respond to 2 weeks of therapy with penicillin G (2 million units IV every 4 h); infections caused by H. influenzae and by strains of Streptococcus pneumoniae that are resistant to penicillin are treated with cefotaxime or ceftriaxone for 2 weeks. Most enteric gram-negative infections can be cured in 3–4 weeks by a second- or third-generation cephalosporin given IV or by a fluoroquinolone such as levofloxacin (500 mg IV or PO every 24 h). P. aeruginosa infection should be treated for at least 2 weeks with a combination regimen composed of an aminoglycoside plus either an extended-spectrum penicillin such as mezlocillin (3 g IV every 4 h) or an antipseudomonal cephalosporin such as ceftazidime (1 g IV every 8 h). If tolerated, this regimen is continued for an additional 2 weeks; alternatively, a fluoroquinolone such as ciprofloxacin (750 mg PO twice daily) is given by itself or with the penicillin or cephalosporin in place of the aminoglycoside.

Timely drainage of pus and necrotic debris from the infected joint is required for a favorable outcome. Needle aspiration of readily accessible joints such as the knee may be adequate if loculations or particulate matter in the joint does not prevent its thorough decompression. Arthroscopic drainage and lavage may be employed initially or within several days if repeated needle aspiration fails to relieve symptoms, decrease the volume of the effusion and the synovial white cell count, and clear bacteria from smears and cultures. In some cases, arthrotomy is necessary to remove loculations and debride infected synovium, cartilage, or bone. Septic arthritis of the hip is best managed with arthrotomy, particularly in young children, in whom infection threatens the viability of the femoral head. Septic joints do not require immobilization except for pain control before symptoms are alleviated by treatment. Weight bearing should be avoided until signs of inflammation have subsided, but frequent passive motion of the joint is indicated to maintain full mobility. Although addition of glucocorticoids to antibiotic treatment improves the outcome of S. aureus arthritis in experimental animals, no clinical trials have evaluated this approach in humans.

GONOCOCCAL ARTHRITIS

Epidemiology

Although its incidence has declined in recent years, gonococcal arthritis has accounted for up to 70% of episodes of infectious arthritis in persons <40 years of age in the United States. Arthritis due to N. gonorrhoeae is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx. Women are at greatest risk during menses and during pregnancy and overall are two to three times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis. Persons with complement deficiencies, especially of the terminal components, are prone to recurrent episodes of gonococcemia. Strains of gonococci that are most likely to cause DGI include those which produce transparent colonies in culture, have the type IA outer-membrane protein, or are of the AUH-auxotroph type.

Clinical manifestations and laboratory findings

The most common manifestation of DGI is a syndrome of fever, chills, rash, and articular symptoms. Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities. Migratory arthritis and tenosynovitis of the knees, hands, wrists, feet, and ankles are prominent. The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues. Thus, cultures of synovial fluid are consistently negative, and blood cultures are positive in fewer than 45% of patients. Synovial fluid may be difficult to obtain from inflamed joints and usually contains only 10,000–20,000 leukocytes/μL.

True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients. A single joint such as the hip, knee, ankle, or wrist is usually involved. Synovial fluid, which contains >50,000 leukocytes/μL, can be obtained with ease; the gonococcus is evident only occasionally in Gram-stained smears, and cultures of synovial fluid are positive in fewer than 40% of cases. Blood cultures are almost always negative.

Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites. NAA-based urine tests also may be positive. Cultures and Gram-stained smears of skin lesions are occasionally positive. All specimens for culture should be plated onto T ayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO_2, as generated in a candle jar. NAA-based assays are extremely sensitive in detecting gonococcal DNA in synovial fluid. A dramatic alleviation of symptoms within 12–24 h af er the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

TREATMENT Gonococcal Arthritis

Initial treatment consists of cef riaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms. Once local and systemic signs are clearly resolving, the 7-day course of therapy can be completed with an oral fluoroquinolone such as ciprofloxacin (500 mg twice daily) if the organism is known to be susceptible. If penicillin-susceptible organisms are isolated, amoxicillin (500 mg three times daily) may be used. Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment. Arthroscopic lavage or arthrotomy is rarely required. Patients with DGI should be treated for Chlamydia trachomatis infection unless this infection is ruled out by appropriate testing.

It is noteworthy that arthritis symptoms similar to those seen in DGI occur in meningococcemia. A dermatitis-arthritis syndrome, purulent monarthritis, and reactive polyarthritis have been described. All respond to treatment with IV penicillin.

SPIROCHETAL ARTHRITIS

LYME DISEASE

Lyme disease due to infection with the spirochete Borrelia burgdor*f*eri causes arthritis in up to 60% of persons who are not treated. Intermittent arthralgias and myalgias—but not arthritis—occur within days or weeks of inoculation of the spirochete by the Ixodes tick. Later, there are three patterns of joint disease: (1) Fif y percent of untreated persons experience intermittent episodes of monarthritis or oligoarthritis involving the knee and/or other large joints. T e symptoms wax and wane without treatment over months, and each year 10–20% of patients report loss of joint symptoms. (2) Twenty percent of untreated persons develop a pattern of waxing and waning arthralgias. (3) Ten percent of untreated patients develop chronic inflammatory synovitis that results in erosive lesions and destruction of the joint. Serologic tests for IgG antibodies to B. burgdor*f*eri are positive in more than 90% of persons with Lyme arthritis, and an NAA-based assay detects Borrelia DNA in 85%.

TREATMENT Lyme Arthritis

Lyme arthritis generally responds well to therapy. A regimen of oral doxycycline (100 mg twice daily for 30 days), oral amoxicillin (500 mg four times daily for 30 days), or parenteral cef riaxone (2 g/d for 2–4 weeks) is recommended. Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy. Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

SYPHILITIC ARTHRITIS

Articular manifestations occur in different stages of syphilis. In early congenital syphilis, periarticular swelling and immobilization of the involved limbs (Parrot's pseudoparalysis) complicate osteochondritis of long bones. Clutton's joint, a late manifestation of congenital syphilis that typically develops between ages 8 and 15 years, is caused by chronic painless synovitis with effusions of large joints, particularly the knees and elbows. Secondary syphilis may be associated with arthralgias, with symmetric arthritis of the knees and ankles and occasionally of the shoulders and wrists, and with sacroiliitis. T e arthritis follows a subacute to chronic course with a mixed mononuclear and neutrophilic synovial-fluid pleocytosis (typical cell counts, 5000–15,000/μL). Immunologic mechanisms may contribute to the arthritis, and symptoms usually improve rapidly with penicillin therapy. In tertiary syphilis, Charcot's joint results from sensory loss due to tabes dorsalis. Penicillin is not helpful in this setting.

MYCOBACTERIAL ARTHRITIS

Tuberculous arthritis accounts for ~1% of all cases of tuberculosis and 10% of extrapulmonary cases. The most common presentation is chronic granulomatous monarthritis. An unusual syndrome, Poncet's disease, is a reactive symmetric form of polyarthritis that affects persons with visceral or disseminated tuberculosis. No mycobacteria are found in the joints, and symptoms resolve with antituberculous therapy.

Unlike tuberculous osteomyelitis, which typically involves the thoracic and lumbar spine (50% of cases), tuberculous arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and only occasionally involves smaller non-weight-bearing joints. Progressive monarticular swelling and pain develop over months or years, and systemic symptoms are seen in only half of all cases. Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts. Coexistent active pulmonary tuberculosis is unusual.

Aspiration of the involved joint yields fluid with an average cell count of 20,000/μL, with ~50% neutrophils. Acid-fast staining of the fluid yields positive results in fewer than one-third of cases, and cultures are positive in 80%. Culture of synovial tissue taken at biopsy is positive in ~90% of cases and shows granulomatous inflammation in most. NAA methods can shorten the time to diagnosis to 1 or 2 days. Radiographs reveal peripheral erosions at the points of synovial attachment, periarticular osteopenia, and eventually joint-space narrowing. Therapy for tuberculous arthritis is the same as that for tuberculous pulmonary disease, requiring the administration of multiple agents for 6–9 months. Therapy is more prolonged in immunosuppressed individuals such as those infected with HIV.

Various atypical mycobacteria found in water and soil may cause chronic indolent arthritis. Such disease results from trauma and direct inoculation associated with farming, gardening, or aquatic activities. Smaller joints, such as the digits, wrists, and knees, are usually involved. Involvement of tendon sheaths and bursae is typical. The mycobacterial species involved include Mycobacterium marinum, M. avium-intracellulare, M. terrae, M. kansasii, M. *f*ortuitum, and M. chelonae. In persons who have HIV infection or are receiving immunosuppressive therapy, hematogenous spread to the joints has been reported for M. kansasii, M. avium complex, and M. haemophilum. Diagnosis usually requires biopsy and culture, and therapy is based on antimicrobial susceptibility patterns.

FUNGAL ARTHRITIS

Fungi are an unusual cause of chronic monarticular arthritis. Granulomatous articular infection with the endemic dimorphic fungi Coccidioides immitis, Blastomyces dermatitidis, and (less commonly) Histoplasma capsulatum **(Fig. 21-2)** results from hematogenous seeding or direct extension from bony lesions in

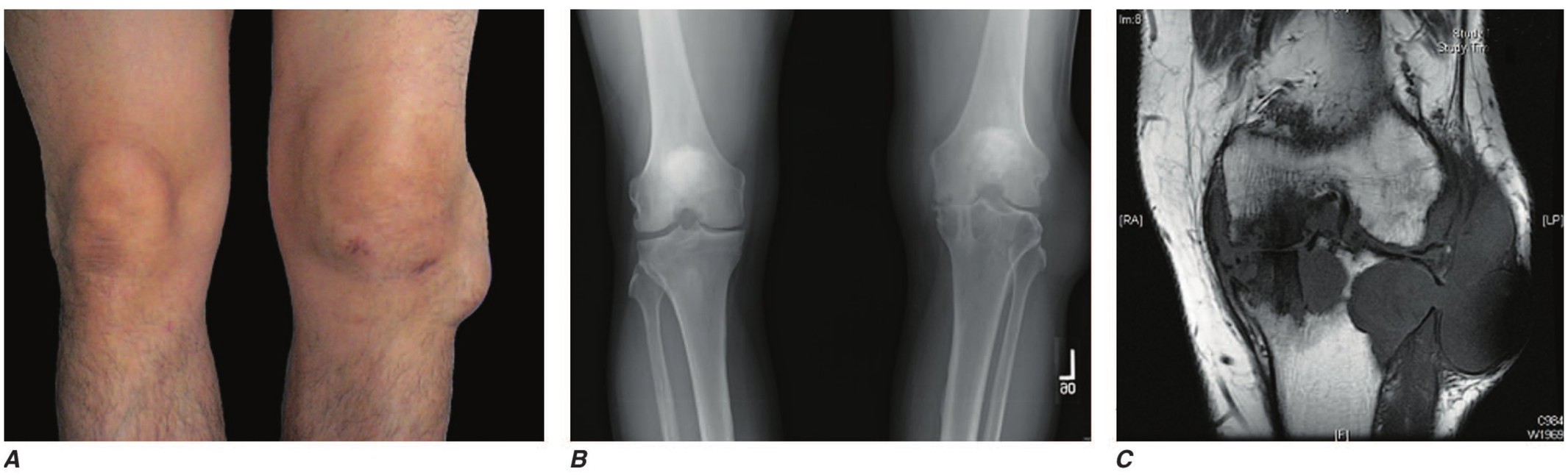


FIGURE 21-2

Chronic arthritis caused by Histoplasma capsulatum in the left knee. A. A man in his sixties from El Salvador presented with a history of progressive knee pain and difficulty walking for several years. He had undergone arthroscopy for a meniscal tear 7 years before presentation (without relief) and had received several intraarticular glucocorticoid injections. The patient developed significant deformity of the knee over time, including a large effusion in the lateral aspect. B. An x-ray of the knee showed multiple abnormalities, including severe medial femorotibial joint-space narrowing, several large subchondral cysts within the tibia and the patellofemoral compartment, a large suprapatellar joint effusion, and a large soft tissue mass projecting laterally over the knee. C. MRI further defined these abnormalities and demonstrated the cystic nature of the lateral knee abnormality. Synovial biopsies demonstrated chronic inflammation with giant cells, and cultures grew H. capsulatum after 3 weeks of incubation. All clinical cystic lesions and the effusion resolved after 1 year of treatment with itraconazole. The patient underwent a left total knee replacement for definitive treatment. (Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.)

persons with disseminated disease. Joint involvement is an unusual complication of sporotrichosis (infection with Sporothrix schenckii) among gardeners and other persons who work with soil or sphagnum moss. Articular sporotrichosis is six times more common among men than among women, and alcoholics and other debilitated hosts are at risk for polyarticular infection.

Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread. Candida infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints. Unusual cases of arthritis due to Aspergillus species, Cryptococcus neoformans, Pseudallescheria boydii, and the dematiaceous fungi also have resulted from direct inoculation or disseminated hematogenous infection in immunocompromised persons. In the United States, a 2012 national outbreak of fungal arthritis (and meningitis) caused by Exserohilum rostratum was linked to intraspinal and intraarticular injection of a contaminated preparation of methylprednisolone acetate.

The synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/μL, with ~70% neutrophils. Stained specimens and cultures of synovial tissue often confirm the diagnosis of fungal arthritis when studies of synovial fluid give negative results. Treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen. The doses and duration of therapy are the same as for disseminated disease. Intraarticular instillation of amphotericin B has been used in addition to IV therapy.

VIRAL ARTHRITIS

Viruses produce arthritis by infecting synovial tissue during systemic infection or by provoking an immunologic reaction that involves joints. As many as 50% of women report persistent arthralgias, and 10% report frank arthritis within 3 days of the rash that follows natural infection with rubella virus and within 2–6 weeks after receipt of live-virus vaccine. Episodes of symmetric inflammation of fingers, wrists, and knees uncommonly recur for >1 year, but a syndrome of chronic fatigue, low-grade fever, headaches, and myalgias can persist for months or years. IV immunoglobulin has been helpful in selected cases. Self-limited monarticular or migratory polyarthritis may develop within 2 weeks of the parotitis of mumps; this sequela is more common among men than among women. Approximately 10% of children and 60% of women develop arthritis after infection with parvovirus B19. In adults, arthropathy sometimes occurs without fever or rash. Pain and stiffness, with less prominent swelling (primarily of the hands but also of the knees, wrists, and ankles), usually resolve within weeks, although a small proportion of patients develop chronic arthropathy.

About 2 weeks before the onset of jaundice, up to 10% of persons with acute hepatitis B develop an immune complex–mediated, serum sickness–like reaction with maculopapular rash, urticaria, fever, and arthralgias. Less common developments include symmetric arthritis involving the hands, wrists, elbows, or ankles and morning stiffness that resembles a flare of rheumatoid arthritis. Symptoms resolve at the time jaundice develops. Many persons with chronic hepatitis C infection report persistent arthralgia or arthritis, both in the presence and in the absence of cryoglobulinemia.



Painful arthritis involving larger joints often accompanies the fever and rash of several arthropod-borne viral infections, including those caused by chikungunya, O'nyong-nyong, Ross River, Mayaro, and Barmah Forest viruses. Symmetric arthritis involving the hands and wrists may occur during the convalescent phase of infection with lymphocytic choriomeningitis virus. Patients infected with an enterovirus frequently report arthralgias, and echovirus has been isolated from patients with acute polyarthritis.

Several arthritis syndromes are associated with HIV infection. Reactive arthritis with painful lower-extremity oligoarthritis often follows an episode of urethritis in HIV-infected persons. HIV-associated reactive arthritis appears to be extremely common among persons with the HLA-B27 haplotype, but sacroiliac joint disease is unusual and is seen mostly in the absence of HLA-B27. Up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis. Painless monarthropathy and persistent symmetric polyarthropathy occasionally complicate HIV infection. Chronic persistent oligoarthritis of the shoulders, wrists, hands, and knees occurs in women infected with human T-lymphotropic virus type I. Synovial thickening, destruction of articular cartilage, and leukemic-appearing atypical lymphocytes in synovial fluid are characteristic, but progression to T cell leukemia is unusual.

PARASITIC ARTHRITIS

Arthritis due to parasitic infection is rare. The guinea worm Dracunculus medinensis may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected.

Hydatid cysts infect bones in 1–2% of cases of infection with Echinococcus granulosus. The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis. In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies. Monarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid. Reactive arthritis has been attributed to hookworm, Strongyloides, Cryptosporidium, and Giardia infection in case reports, but confirmation is required.

POSTINFECTIOUS OR REACTIVE ARTHRITIS

Reactive polyarthritis develops several weeks after ~1% of cases of nongonococcal urethritis and 2% of enteric infections, particularly those due to Yersinia enterocolitica, Shigella flexneri, Campylobacter jejuni, and Salmonella species. Only a minority of these patients have the other findings of classic reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash. Studies have identified microbial DNA or antigen in synovial fluid or blood, but the pathogenesis of this condition is poorly understood.

Reactive arthritis is most common among young men (except after Yersinia infection) and has been linked to the HLA-B27 locus as a potential genetic predisposing factor. Patients report painful, asymmetric oligoarthritis that affects mainly the knees, ankles, and feet. Low-back pain is common, and radiographic evidence of sacroiliitis is found in patients with long-standing disease. Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis. Anti-inflammatory agents help relieve symptoms, but the role of prolonged antibiotic therapy in eliminating microbial antigen from the synovium is controversial.

Migratory polyarthritis and fever constitute the usual presentation of acute rheumatic fever in adults **(Chap. 7)**. This presentation is distinct from that of poststreptococcal reactive arthritis, which also follows infections with group A Streptococcus but is not migratory, lasts beyond the typical 3-week maximum of acute rheumatic fever, and responds poorly to aspirin.

INFECTIONS IN PROSTHETIC JOINTS

Infection complicates 1–4% of total joint replacements. The majority of infections are acquired intraoperatively or immediately postoperatively as a result of wound breakdown or infection; less commonly, these joint infections develop later after joint replacement and are the result of hematogenous spread or direct inoculation. The presentation may be acute, with fever, pain, and local signs of inflammation, especially in infections due to S. aureus, pyogenic streptococci, and enteric bacilli. Alternatively, infection may persist for months or years without causing constitutional symptoms when less virulent organisms, such as coagulase-negative staphylococci or diphtheroids, are involved. Such indolent infections usually are acquired during joint implantation and are discovered during evaluation of chronic unexplained pain or after a radiograph shows loosening of the prosthesis; the erythrocyte sedimentation rate and C-reactive protein level are usually elevated in such cases.

The diagnosis is best made by needle aspiration of the joint; accidental introduction of organisms during aspiration must be avoided meticulously. Synovial fluid pleocytosis with a predominance of polymorphonuclear leukocytes is highly suggestive of infection, since other inflammatory processes uncommonly affect prosthetic joints. Culture and Gram's stain usually yield the responsible pathogen. Sonication of explanted prosthetic material can improve the yield of culture, presumably by breaking up bacterial biofilms on the surfaces of prostheses. Use of special media for unusual pathogens such as fungi, atypical mycobacteria, and Mycoplasma may be necessary if routine and anaerobic cultures are negative.

TREATMENT Prosthetic Joint Infections

Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved. In most cases, the prosthesis must be replaced to cure the infection. Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame. In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation. Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis. In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be drained vigorously by open arthrotomy or arthroscopically. In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, suppression of the infection with antibiotics may be a reasonable goal. A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and ciprofloxacin is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration. This is approach, which is based on the ability of rifampin to kill organisms adherent to foreign

material and in the stationary growth phase, requires confirmation in prospective trials.

PREVENTION

To avoid the disastrous consequences of infection, candidates for joint replacement should be selected with care. Rates of infection are particularly high among patients with rheumatoid arthritis, persons who have undergone previous surgery on the joint, and persons with medical conditions requiring immunosuppressive therapy. Perioperative antibiotic prophylaxis, usually with cefazolin, and measures to decrease intraoperative contamination, such as laminar flow, have lowered the rates of perioperative infection to <1% in many centers. After implantation, measures should be taken to prevent or rapidly treat extraarticular infections that might give rise to hematogenous spread to the prosthesis. The effectiveness of prophylactic antibiotics for the prevention of hematogenous infection after dental procedures has not been demonstrated; in fact, viridans streptococci and other components of the oral flora are extremely unusual causes of prosthetic joint infection. Accordingly, the American Dental Association and the American Academy of Orthopaedic Surgeons do not recommend antibiotic prophylaxis for most dental patients with total joint replacements and have stated that there is no convincing evidence to support its use. Similarly, guidelines issued by the American Urological Association and the American Academy of Orthopaedic Surgeons do not recommend the use of prophylactic antibiotics for most patients with prosthetic joints who are undergoing urologic procedures but state that prophylaxis should be considered in certain situations—e.g., for patients (especially immunocompromised patients) who are undergoing a procedure posing a relatively high risk of bacteremia (such as lithotripsy or surgery involving bowel segments).

Acknowledgments

The contributions of James H. Maguire and the late Scott J. Taler to this chapter in earlier editions are gratefully acknowledged.

CHAPTER 22

FIBROMYALGIA

Leslie J. Crofford

DEFINITION

Fibromyalgia (FM) is characterized by chronic widespread musculoskeletal pain and tenderness. Although FM is defined primarily as a pain syndrome, patients also commonly report associated neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Patients with FM have an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes. Available evidence implicates the central nervous system as key to maintaining pain and other core symptoms of FM and related conditions. The presence of FM is associated with substantial negative consequences for physical and social functioning.

EPIDEMIOLOGY

In clinical settings, a diagnosis of FM is made in 2% of the population and is far more common in women than in men, with a ratio of 9:1. However, in population-based survey studies worldwide, the prevalence rate is 2–5%, with a female-to-male ratio of only 2–3:1 and with some variability depending on the method of ascertainment. The prevalence data are similar across socioeconomic classes. Cultural factors may play a role in determining whether patients with FM symptoms seek medical attention; however, even in cultures in which secondary gain is not expected to play a significant role, the prevalence of FM remains in this range.

CLINICAL MANIFESTATIONS

Pain and tenderness

At presentation, patients with FM most commonly report "pain all over." These patients have pain that is typically both above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to FM is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity. For a diagnosis of FM, pain should have been present most of the day on most days for at least 3 months.

The clinical pain of FM is associated with increased evoked pain sensitivity. In clinical practice, this elevated sensitivity may be determined by a tender-point examination in which the examiner uses the thumbnail to exert pressure of 4 kg/m^2 (or the amount of pressure leading to blanching of the tip of the thumbnail) on well-defined musculotendinous sites **(Fig. 22-1)**. Previously, the classification criteria of the American College of Rheumatology required that 11 of 18 sites be perceived as painful for a diagnosis of FM. In practice, tenderness is a continuous variable, and strict application of a categorical threshold for diagnostic specifics is not necessary. Newer criteria eliminate the need for tender points and focus instead on clinical symptoms of widespread pain and neuropsychological symptoms. The newer criteria perform well in a clinical setting in comparison to the older, tender-point criteria. However, it appears that when the new criteria are applied to populations, the result is an increase in prevalence of FM and a change in the sex ratio (see "Epidemiology," earlier).

Patients with FM often have peripheral pain generators that are thought to serve as triggers for the more widespread pain attributed to central nervous system factors. Potential pain generators such as arthritis, bursitis, tendinitis, neuropathies, and other inflammatory or degenerative conditions should be identified by history and physical examination. More subtle pain generators may include joint hypermobility and scoliosis. In addition, patients may have chronic myalgias triggered by infectious, metabolic, or psychiatric conditions that can also serve as triggers for the development of FM. These conditions are often identified in the differential

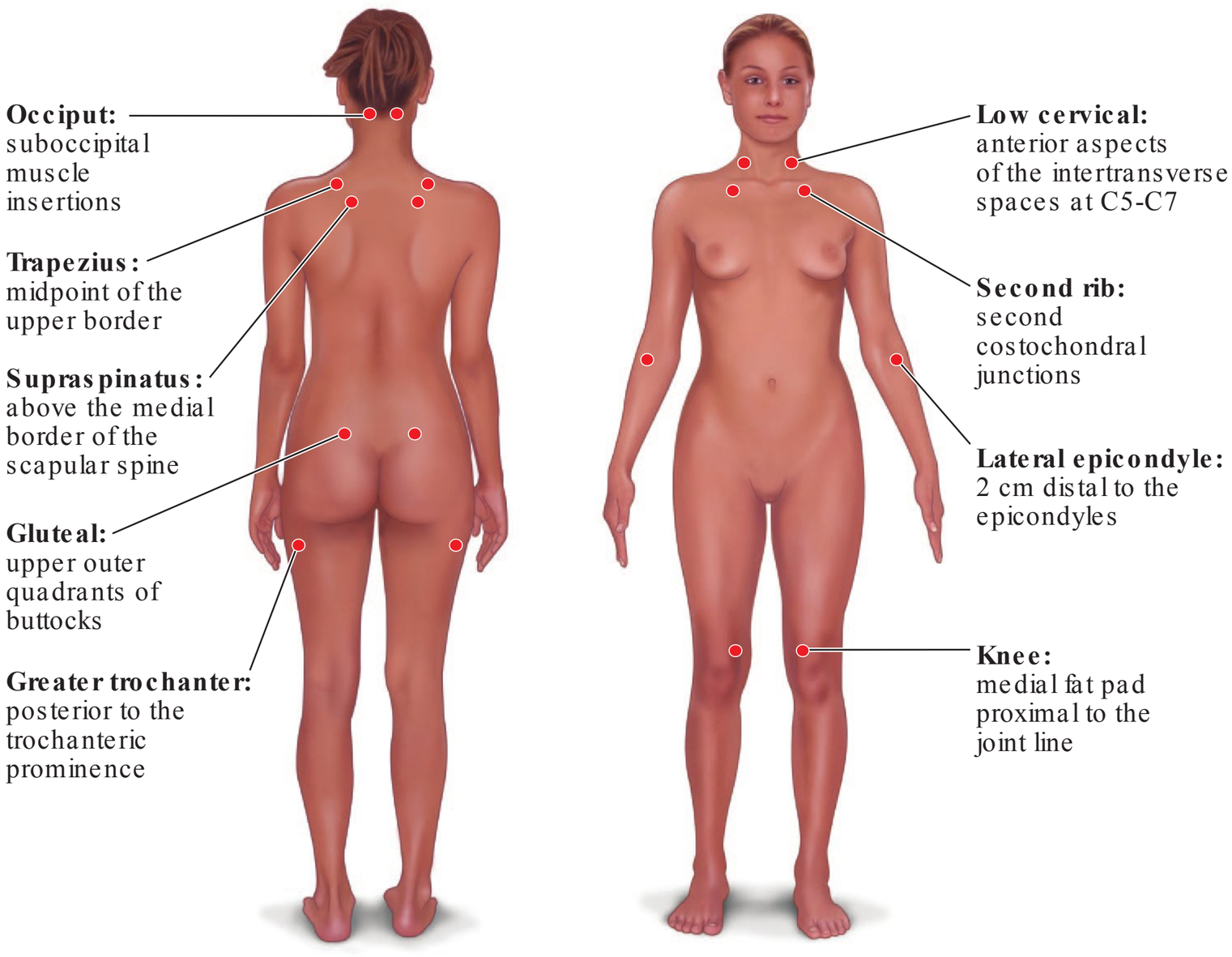


FIGURE 22-1
Tender-point assessment in patients with fibromyalgia. (Figure created using data from F Wolfe et al: Arthritis Care Res 62:600, 2010.)

diagnosis of patients with FM, and a major challenge is to distinguish the ongoing activity of a triggering condition from FM that is occurring as a consequence of a comorbid condition and that should itself be treated.

Neuropsychological symptoms

In addition to widespread pain, FM patients typically report fatigue, stiffness, sleep disturbance, cognitive dysfunction, anxiety, and depression. These symptoms are present to varying degrees in most FM patients but are not present in every patient or at all times in a given patient. Relative to pain, such symptoms may, however, have an equal or even greater impact on function and quality of life. Fatigue is highly prevalent in patients under primary care who ultimately are diagnosed with FM. Pain, stiffness, and fatigue often are worsened by exercise or unaccustomed activity (postexertional malaise). The sleep complaints include difficulty falling asleep, difficulty staying asleep, and early-morning awakening. Regardless of the specific complaint, patients awake feeling unrefreshed. Patients with FM may meet criteria for restless legs syndrome and sleep-disordered breathing; frank sleep apnea can also be documented. Cognitive issues are characterized as slowness in processing, difficulties with attention or concentration, problems with word retrieval, and short-term memory loss. Studies have demonstrated altered cognitive function in these domains in patients with FM, though speed of processing is age-appropriate. Symptoms of anxiety and depression are common, and the lifetime prevalence of mood disorders in patients with FM approaches 80%. Although depression is neither necessary nor sufficient for the diagnosis of FM, it is important to screen for major depressive disorders by querying for depressed mood and anhedonia. Analysis of genetic factors that are likely to predispose to FM reveals shared neurobiologic pathways with mood disorders, providing the basis for comorbidity (see later in this chapter).

Overlapping syndromes

Because FM can overlap in presentation with other chronic pain conditions, review of systems often reveals headaches, facial/jaw pain, regional myofascial pain particularly involving the neck or back, and arthritis. Visceral pain involving the gastrointestinal tract, bladder, and pelvic or perineal region is often present as well. Patients may or may not meet defined criteria for specific syndromes. It is important for patients to understand that shared pathways may mediate symptoms and that treatment strategies effective for one condition may help with global symptom management.

Comorbid conditions

FM is often comorbid with chronic musculoskeletal, infectious, metabolic, or psychiatric conditions. Whereas FM affects only 2–5% of the general population, it occurs in 20% or more of patients with degenerative or inflammatory rheumatic disorders, likely because these conditions serve as peripheral pain generators to alter central pain-processing pathways. Similarly, chronic infectious, metabolic, or psychiatric diseases associated with musculoskeletal pain can mimic FM and/or serve as a trigger for the development of FM. It is particularly important for clinicians to be sensitive to pain management of these comorbid conditions so that when FM emerges—characterized by pain outside the boundaries of what could reasonably be explained by the triggering condition, development of neuropsychological symptoms, or tenderness on physical examination—treatment of central pain processes will be undertaken as opposed to a continued focus on treatment of peripheral or inflammatory causes of pain.

Psychosocial considerations

Symptoms of FM often have their onset and are exacerbated during periods of high-level real or perceived stress. T is pattern may reflect an interaction among central stress physiology, vigilance or anxiety, and central pain-processing pathways. An understanding of current psychosocial stressors will aid in patient management, as many factors that exacerbate symptoms cannot be addressed by pharmacologic approaches. Furthermore, there is a high prevalence of exposure to previous interpersonal and other forms of violence in patients with FM and related conditions. If posttraumatic stress disorder is an issue, the clinician should be aware of it and consider treatment options.

Functional impairment

It is crucial to evaluate the impact of FM symptoms on function and role fulfillment. In defining the success of a management strategy, improved function is a key measure. Functional assessment should include physical, mental, and social domains. A recognition of the ways in which role functioning falls short will be helpful in the establishment of treatment goals.

DIFFERENTIAL DIAGNOSIS

Because musculoskeletal pain is such a common complaint, the differential diagnosis of FM is broad. **Table 22-1** lists some of the more common conditions that should be considered. Patients with inflammatory causes for widespread pain should be identifiable on the basis of specific history, physical findings, and laboratory or radiographic tests.

TABLE 22-1

COMMON CONDITIONS IN THE DIFFERENTIAL DIAGNOSIS OF FIBROMYALGIA

Inflammatory
Polymyalgia rheumatica
Inflammatory arthritis: rheumatoid arthritis, spondyloarthritides
Connective tissue diseases: systemic lupus erythematosus, Sjögren's syndrome
Infectious
Hepatitis C
HIV infection
Lyme disease
Parvovirus B19 infection
Epstein-Barr virus infection
Noninflammatory
Degenerative joint/spine/disk disease
Myofascial pain syndromes
Bursitis, tendinitis, repetitive strain injuries
Endocrine
Hypo- or hyperthyroidism
Hyperparathyroidism
Neurologic Diseases
Multiple sclerosis
Neuropathic pain syndromes
Psychiatric Disease
Major depressive disorder
Drugs
Statins
Aromatase inhibitors

LABORATORY OR RADIOGRAPHIC TESTING

Routine laboratory and radiographic tests yield normal results in FM. T us diagnostic testing is focused on exclusion of other diagnoses and evaluation for pain generators or comorbid conditions **(Table 22-2)**. Most patients with new chronic widespread pain should be assessed for the most common entities in the differential diagnosis. Radiographic testing should be used sparingly and only for diagnosis of inflammatory arthritis. After the patient has been evaluated thoroughly, repeat testing is discouraged unless the symptom complex changes. Particularly to be discouraged is advanced imaging (MRI) of the spine unless there are features suggesting inflammatory spine disease or neurologic symptoms.

GENETICS AND PHYSIOLOGY



As in most complex diseases, it is likely that a number of genes contribute to vulnerability to the development of FM. To date, these genes appear to

TABLE 22-2

LABORATORY AND RADIOGRAPHIC TESTING IN PATIENTS WITH FIBROMYALGIA SYMPTOMS
Routine
Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
Complete blood count (CBC)
Thyroid-stimulating hormone (TSH)
Guided by History and Physical Examination
Complete metabolic panel
Antinuclear antibody (ANA)
Anti-SSA (anti–Sjögren's syndrome A) and anti-SSB
Rheumatoid factor and anti–cyclic citrullinated peptide (anti-CCP)
Creatine phosphokinase (CPK)
Viral and bacterial serologies
Spine and joint radiographs

Source: LM Arnold et al: J Women's Health 21:231, 2012; MA Fitzcharles et al: J Rheumatol 40:1388, 2013.

be in pathways controlling pain and stress responses. Some of the genetic underpinnings of FM are shared across other chronic pain conditions. Genes associated with metabolism, transport, and receptors of serotonin and other monoamines have been implicated in FM and overlapping conditions. Genes associated with other pathways involved in pain transmission have also been described as vulnerability factors for FM. Taken together, the pathways in which polymorphisms have been identified in FM patients further implicate central factors in mediation of the physiology that leads to the clinical manifestations of FM.

Psychophysical testing of patients with FM has demonstrated altered sensory afferent pain processing and impaired descending noxious inhibitory control leading to hyperalgesia and allodynia. Functional MRI and other research imaging procedures clearly demonstrate activation of the brain regions involved in the experience of pain in response to stimuli that are innocuous in study participants without FM. Pain perception in FM patients is influenced by the emotional and cognitive dimensions, such as catastrophizing and perceptions of control, providing a solid basis for recommendations for cognitive and behavioral treatment strategies.

APPROACH TO THE PATIENT: Fibromyalgia

FM is common and has an extraordinary impact on the patient's function and health-related quality of life. However, its symptoms and impact can be managed effectively by physicians and other health professionals. Developing a partnership with patients is essential for improving the outcome of FM, with a goal of understanding the factors involved, implementing a treatment strategy, and choosing appropriate nonpharmacologic and pharmacologic treatments.

TREATMENT Fibromyalgia

NONPHARMACOLOGIC TREATMENT Patients with chronic pain, fatigue, and other neuropsychological symptoms require a framework for understanding the symptoms that have such an important impact on their function and quality of life. Explaining the genetics, triggers, and physiology of FM can be an important adjunct in relieving associated anxiety and in reducing the overall cost of health care resources. In addition, patients must be educated regarding expectations for treatment. The physician should focus on improved function and quality of life rather than elimination of pain. Illness behaviors, such as frequent physician visits, should be discouraged and behaviors that focus on improved function strongly encouraged.

Treatment strategies should include physical conditioning, with encouragement to begin at low levels of aerobic exercise and to proceed with slow but consistent advancement. Patients who have been physically inactive or who report postexertional malaise may do best in supervised or water-based programs at the start. Activities that promote improved physical function with relaxation, such as yoga and Tai Chi, may also be helpful. Strength training may be recommended after patients reach their aerobic goals. Exercise programs are helpful in reducing tenderness and enhancing self-efficacy. Cognitive-behavioral strategies to improve sleep hygiene and reduce illness behaviors can also be helpful in management.

PHARMACOLOGIC APPROACHES It is essential for the clinician to treat any comorbid triggering condition and to clearly delineate for the patient the treatment goals for each medication. For example, glucocorticoids or nonsteroidal anti-inflammatory drugs may be useful for management of inflammatory triggers but are not effective against FM-related symptoms. At present, the treatment approaches that have proved most successful in FM patients target afferent or descending pain pathways. **Table 22-3** lists the drugs with demonstrated effectiveness. It should be emphasized strongly that opioid analgesics are to be avoided in patients with FM. These agents have no demonstrated efficacy in FM and are associated with opioid-induced hyperalgesia that can worsen both symptoms and function. Use of single agents to treat multiple symptom domains is strongly encouraged. For example, if a patient's symptom complex is dominated by pain and sleep disturbance, use of an agent that exerts both analgesic and sleep-promoting effects is desirable. These agents

TABLE 22-3

PHARMACOLOGIC AGENTS EFFECTIVE FOR TREATMENT OF FIBROMYALGIA

Antidepressants: balanced serotonin–norepinephrine reuptake inhibitors
- Amitryptiline[a]
- Duloxetine[b,c]
- Milnacipran[b,c]

Anticonvulsants: ligands of the alpha-2-delta subunit of voltage-gated calcium channels
- Gabapentin
- Pregabalin[b]

[a]RA Moore et al: Cochrane Database Syst Rev 12:CD008242, 2012.
[b]Approved by the U.S. Food and Drug Administration.
[c]W Hauser et al: Cochrane Database Syst Rev 1: CD010292, 2013.
Source: LM Arnold: Arthritis Rheum 56:1336, 2007.

include sedating antidepressants such as amitriptyline and alpha-2-delta ligands such as gabapentin and pregabalin. For patients whose pain is associated with fatigue, anxiety, or depression, drugs that have both analgesic and antidepressant/anxiolytic effects, such as duloxetine or milnacipran, may be the best first choice.

CHAPTER 23

ARTHRITIS ASSOCIATED WITH SYSTEMIC DISEASE, AND OTHER ARTHRITIDES

Carol A. Langford ■ Brian F. Mandell

ARTHRITIS ASSOCIATED WITH SYSTEMIC DISEASE

ARTHROPATHY OF ACROMEGALY

Acromegaly is the result of excessive production of growth hormone by an adenoma in the anterior pituitary gland. T e excessive secretion of growth hormone along with insulin-like growth factor I stimulates proliferation of cartilage, periarticular connective tissue, and bone, resulting in several musculoskeletal problems, including osteoarthritis, back pain, muscle weakness, and carpal tunnel syndrome.

Osteoarthritis is a common feature, most often affecting the knees, shoulders, hips, and hands. Single or multiple joints may be affected. Hypertrophy of cartilage initially produces radiographic widening of the joint space. T e newly synthesized cartilage is abnormally susceptible to fissuring, ulceration, and destruction. Ligamental laxity of joints further contributes to the development of osteoarthritis. Cartilage degrades, the joint space narrows, and subchondral sclerosis and osteophytes develop. Joint examination reveals crepitus and laxity. Joint fluid is noninflammatory. Calcium pyrophosphate dihydrate crystals are found in the cartilage in some cases of acromegaly arthropathy and, when shed into the joint, can elicit attacks of pseudogout. Chondrocalcinosis may be observed on radiographs. Back pain is extremely common, perhaps as a result of spine hypermobility. Spine radiographs show normal or widened intervertebral disk spaces, hypertrophic anterior osteophytes, and ligamental calcification. T e latter changes are similar to those observed in patients with diffuse idiopathic skeletal hyperostosis. Dorsal kyphosis in conjunction with elongation of the ribs contributes to the development of the barrel chest seen in acromegalic patients. T e hands and feet become enlarged as a result of soft tissue proliferation. T e fingers are thickened and have spadelike distal tufts. One-third of patients have a thickened heel pad. Approximately 25% of patients exhibit Raynaud's phenomenon. Carpal tunnel syndrome occurs in about half of patients. T e median nerve is compressed by excess connective tissue in the carpal tunnel. Patients with acromegaly may develop proximal muscle weakness, which is thought to be caused by the effect of growth hormone on muscle. Serum muscle enzyme levels and electromyographic findings are normal. Muscle biopsy specimens contain muscle fibers of varying size without inflammation.

ARTHROPATHY OF HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage. Absorption of excessive amounts of iron from the intestine leads to iron deposition in parenchymal cells, which results in impairment of organ function. Symptoms of hemochromatosis usually begin between the ages of 40 and 60 but can appear earlier. Arthropathy, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. T e arthropathy is an osteoarthritis-like disorder affecting the small joints of the hands and later the larger joints, such as knees, ankles, shoulders, and hips. T e second and third metacarpophalangeal joints of both hands are often the first and most prominent joints affected; this clinical picture may provide an important clue to the possibility of hemochromatosis because these joints are not predominantly affected by "routine" osteoarthritis. Patients experience some morning stiffness and pain with use of involved joints. T e affected joints are enlarged and mildly tender. Radiographs show narrowing of the joint space, subchondral sclerosis, subchondral cysts, and juxtaarticular proliferation of bone. Hooklike osteophytes are seen in

up to 20% of patients; although they are regarded as a characteristic feature of hemochromatosis, they can also occur in osteoarthritis and are not disease specific. T e synovial fluid is noninflammatory. T e synovium shows mild to moderate proliferation of iron-containing lining cells, fibrosis, and some mononuclear cell infiltration. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease, and some patients late in the course of disease experience episodes of acute pseudogout (**Chap. 20**). An early diagnosis is suggested by high serum transferrin saturation, which is more sensitive than ferritin elevation.

Iron may damage the articular cartilage in several ways. Iron catalyzes superoxide-dependent lipid peroxidation, which may play a role in joint damage. In animal models, ferric iron has been shown to interfere with collagen formation and increase the release of lysosomal enzymes from cells in the synovial membrane. Iron inhibits synovial tissue pyrophosphatase in vitro and therefore may inhibit pyrophosphatase in vivo, resulting in chondrocalcinosis.

TREATMENT Arthropathy of Hemochromatosis

T e treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little effect on established arthritis, which, along with chondrocalcinosis, may progress. Symptom-based treatment of the arthritis consists of administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as tolerated. Acute pseudogout attacks are treated with high doses of an NSAID or a short course of glucocorticoids. Hip or knee total joint replacement has been successful in advanced disease.

HEMOPHILIC ARTHROPATHY

Hemophilia is a sex-linked recessive genetic disorder characterized by the absence or deficiency of factor VIII (hemophilia A, or classic hemophilia) or factor IX (hemophilia B, or Christmas disease). Hemophilia A constitutes 85% of cases. Spontaneous hemarthrosis is a common problem with both types of hemophilia and can lead to a deforming arthritis. T e frequency and severity of hemarthrosis are related to the degree of clotting factor deficiency. Hemarthrosis is not common in other disorders of coagulation such as von Willebrand disease, factor V deficiency, warfarin therapy, or thrombocytopenia.

Hemarthrosis occurs after 1 year of age, when a child begins to walk and run. In order of frequency, the joints most commonly affected are the knees, ankles, elbows, shoulders, and hips. Small joints of the hands and feet are occasionally involved.

In the initial stage of arthropathy, hemarthrosis produces a warm, tensely swollen, and painful joint. T e patient holds the affected joint in flexion and guards against any movement. Blood in the joint remains liquid because of the absence of intrinsic clotting factors and the absence of tissue thromboplastin in the synovium. T e synovial blood is resorbed over a period of ≥1 week, with the precise interval depending on the size of the hemarthrosis. Joint function usually returns to normal or baseline in~2 weeks. Low-grade temperature elevation may accompany hemarthrosis, but a fever >101°F (38.3°C) warrants concern about infection.

Recurrent hemarthrosis may result in chronic arthritis. T e involved joints remain swollen, and flexion deformities develop. Joint motion may be restricted and function severely limited. Restricted joint motion or laxity with subluxation is a feature of end-stage disease.

Bleeding into muscle and soft tissue also causes musculoskeletal dysfunction. When bleeding into the iliopsoas muscle occurs, the hip is held in flexion because of the pain, resulting in a hip flexion contracture. Rotation of the hip is preserved, which distinguishes this problem from hemarthrosis or other causes of hip synovitis. Expansion of the hematoma may place pressure on the femoral nerve, resulting in femoral neuropathy. Hemorrhage into a closed compartment space, such as the calf or the volar compartment in the forearm, can result in muscle necrosis, neuropathy, and flexion deformities of the ankles, wrists, and fingers. When bleeding involves periosteum or bone, a painful pseudotumor forms. T ese pseudotumors occur distal to the elbows or knees in children and improve with treatment of hemophilia. Surgical removal is indicated if the pseudotumor continues to enlarge. In adults, pseudotumors develop in the femur and pelvis and are usually refractory to treatment. When bleeding occurs in muscle, cysts may develop within the muscle. Needle aspiration of a cyst is contraindicated because this procedure can induce further bleeding; however, if the cyst becomes secondarily infected, drainage may be necessary (after factor repletion).

Septic arthritis is rare in hemophilia and is dif cult to distinguish from acute hemarthrosis on physical examination. If there is serious suspicion of an infected joint, the joint should be aspirated immediately, the fluid cultured, and treatment with broad-spectrum antibiotics administered, with coverage for microorganisms including Staphylococcus, until culture results become available. Clotting-factor deficiency should be corrected before arthrocentesis to minimize the risk of traumatic bleeding.

Radiographs of joints reflect the stage of disease. In early stages, there is only capsule distention; later, juxtaarticular osteopenia, marginal erosions, and subchondral cysts develop. Late in the disease, the joint space is narrowed and there is bony overgrowth similar to that in osteoarthritis.

TREATMENT Hemarthrosis

The treatment of musculoskeletal bleeding is initiated with the immediate infusion of factor VIII or IX at the first sign of joint or muscle hemorrhage. Patients who have developed factor inhibitors are at elevated risk for joint damage and may benefit from receiving recombinant activated factor VII or activated prothrombin complex concentrate. The joint should be rested in a position of forced extension, as tolerated, to avoid contracture. Analgesia should be provided; nonselective NSAIDs, which can diminish platelet function, should be avoided if possible. Selective cyclooxygenase-2 inhibitors do not interfere with platelet function, although cardiovascular and gastrointestinal risks must still be weighed. Synovectomy—open or arthroscopic—may be attempted in patients with chronic symptomatic synovial proliferation and recurrent hemarthrosis, although hypertrophied synovium is highly vascular and subject to bleeding. Both types of synovectomy reduce the number of hemarthroses. Open surgical synovectomy, however, is associated with some loss of range of motion. Both require aggressive prophylaxis against bleeding. Radiosynovectomy with either yttrium 90 silicate or phosphorus 31 colloid has been effective and may be attempted when surgical synovectomy is not practical. Total joint replacement is indicated for severe joint destruction and incapacitating pain.

ARTHROPATHIES ASSOCIATED WITH HEMOGLOBINOPATHIES

Sickle cell disease

Sickle cell disease is associated with several musculoskeletal abnormalities **(Table 23-1)**. Children under the age of 5 years may develop diffuse swelling, tenderness, and warmth of the hands and feet lasting 1–3 weeks. This condition, referred to as sickle cell dactylitis or hand-foot syndrome, has also been observed in sickle cell thalassemia. Dactylitis is believed to result from infarction of the bone marrow and cortical bone leading to periostitis and soft tissue swelling. Radiographs show periosteal elevation, subperiosteal new-bone formation, and areas of radiolucency and increased density involving the metacarpals, metatarsals, and proximal phalanges. These bone changes disappear after several months. The syndrome leaves little or no residual damage. Because hematopoiesis ceases in the small bones of the hands and feet with age, the syndrome is rarely seen after age 5.

Sickle cell crisis is associated with periarticular pain and occasionally with joint effusions. The joint and periarticular area are warm and tender. Knees and elbows are most often affected, but other joints can be involved. Joint effusions are usually noninflammatory. Acute synovial infarction can cause a sterile effusion with high neutrophil counts in synovial fluid. Synovial biopsies have shown mild lining-cell proliferation and microvascular thrombosis with infarctions. Scintigraphic studies have shown decreased marrow uptake adjacent to the involved joint.

Patients with sickle cell disease seem predisposed to osteomyelitis, which commonly involves the long tubular bones; Salmonella is a particularly common cause. Radiographs of the involved site initially show periosteal elevation, with subsequent disruption of the cortex. Treatment of the infection results in healing of the bone lesion. In addition, sickle cell disease is associated with bone infarction resulting from vaso-occlusion secondary to the sickling of red cells. Bone infarction also occurs in hemoglobin sickle cell disease and sickle cell thalassemia. The bone pain in sickle cell crisis is due to infarction of bone and bone marrow. In children, infarction of the epiphyseal growth plate interferes with normal growth of the affected extremity. Radiographically, infarction of the bone cortex results in periosteal elevation and irregular thickening of the bone cortex. Infarction in the bone marrow leads to lysis, fibrosis, and new bone formation. Clinical distinction between osteomyelitis and bone infarctions can be difficult; imaging can be helpful.

Avascular necrosis of the head of the femur occurs in ~5% of patients. It also occurs in the humeral head and less commonly in the distal femur, tibial condyles, distal radius, vertebral bodies, and other juxtaarticular sites. Irregularity of the femoral head and other articular surfaces often results in degenerative joint disease. Radiography of the affected joint may show patchy radiolucency and density followed by flattening of the bone. MRI is a sensitive technique for detecting early avascular necrosis as well as bone infarction elsewhere. Total hip replacement and placement of prostheses in other joints may improve function and relieve joint pain in these patients.

Septic arthritis is occasionally encountered in sickle cell disease **(Chap. 21)**. Multiple joints may be infected.

TABLE 23-1

MUSCULOSKELETAL ABNORMALITIES IN SICKLE CELL DISEASE

SICKLE CELL DACTYLITIS	AVASCULAR NECROSIS
Joint effusions in sickle cell crises	Bone changes secondary to marrow hyperplasia
Osteomyelitis	
Infarction of bone	Septic arthritis
Infarction of bone marrow	Gouty arthritis

Joint infection may result from bacteremia due to splenic dysfunction or from contiguous osteomyelitis. T e more common microorganisms include Staphylococcus aureus, Streptococcus, and Salmonella. Salmonella does not cause septic arthritis as frequently as it causes osteomyelitis. Acute gouty arthritis is uncommon in sickle cell disease, even though 40% of patients are hyperuricemic. However, it may occur in patients generally not expected to get gout (young patients, female patients). Hyperuricemia is due to overproduction of uric acid secondary to increased red cell turnover as well as suboptimal renal excretion. Attacks may be polyarticular, and diagnostic arthrocentesis should be performed to distinguish infection from gout or synovial infarction.

T e bone marrow hyperplasia in sickle cell disease results in widening of the medullary cavities, thinning of the cortices, and coarse trabeculations and central cupping of the vertebral bodies. T ese changes are also seen to a lesser degree in hemoglobin sickle cell disease and sickle cell thalassemia. In normal individuals red marrow is located mostly in the axial skeleton, but in sickle cell disease red marrow is found in the bones of the extremities and even in the tarsal and carpal bones. Vertebral compression may lead to dorsal kyphosis, and softening of the bone in the acetabulum may result in protrusio acetabuli.

Thalassemia

A congenital disorder of hemoglobin synthesis, β thalassemia is characterized by impaired production of β chains. Bone and joint abnormalities occur in β thalassemia, being most common in the major and intermedia groups. In one study, ~50% of patients with β thalassemia had evidence of symmetric ankle arthropathy characterized by a dull aching pain that was aggravated by weight bearing. T e onset came most often in the second or third decade of life. T e degree of ankle pain in these patients varied. Some patients experienced self-limited ankle pain that occurred only after strenuous physical activity and lasted several days or weeks. Other patients had chronic ankle pain that became worse with walking. Symptoms eventually abated in a few patients. Compression of the ankle, calcaneus, or forefoot was painful in some patients. Synovial fluid from two patients was noninflammatory. Radiographs of the ankle showed osteopenia, widened medullary spaces, thin cortices, and coarse trabeculations—findings that are largely the result of bone marrow expansion. T e joint space was preserved. Specimens of bone from three patients revealed osteomalacia, osteopenia, and microfractures. Increased numbers of osteoblasts as well as increased foci of bone resorption were present on the bone surface. Iron staining was found in the bone trabeculae, in osteoid, and in the cement line. Synovium showed hyperplasia of lining cells, which contained deposits of hemosiderin. T is arthropathy was considered to be related to the underlying bone pathology. T e role of iron overload or abnormal bone metabolism in the pathogenesis of this arthropathy is not known. T e arthropathy was treated with analgesics and splints. Patients also received transfusions to decrease hematopoiesis and bone marrow expansion.

In patients with β-thalassemia major and β-thalassemia intermedia, other joints are also involved, including the knees, hips, and shoulders. Acquired hemochromatosis with arthropathy has been described in a patient with thalassemia. Gouty arthritis and septic arthritis can occur. Avascular necrosis is not a feature of thalassemia because there is no sickling of red cells leading to thrombosis and infarction.

β-T alassemia minor (also known as β-thalassemia trait) is likewise associated with joint manifestations. Chronic seronegative oligoarthritis affecting predominantly ankles, wrists, and elbows has been described; the affected patients had mild persistent synovitis without large effusions or joint erosions. Recurrent episodes of acute asymmetric arthritis have also been reported; episodes last <1 week and may affect the knees, ankles, shoulders, elbows, wrists, and metacarpal phalangeal joints. T e mechanism underlying this arthropathy is unknown. Treatment with NSAIDs is not particularly effective.

MUSCULOSKELETAL DISORDERS ASSOCIATED WITH HYPERLIPIDEMIA

Musculoskeletal or cutaneous manifestations may be the first clinical indication of a specific hereditary disorder of lipoprotein metabolism. Patients with familial hypercholesterolemia (previously referred to as type II hyperlipoproteinemia) may have recurrent migratory polyarthritis involving the knees and other large peripheral joints and, to a lesser degree, peripheral small joints. Pain ranges from moderate to incapacitating. T e involved joints can be warm, erythematous, swollen, and tender. Arthritis usually has a sudden onset, lasts from a few days to 2 weeks, and does not cause joint damage. Episodes may suggest acute gout attacks. Several attacks occur per year. Synovial fluid from involved joints is not inflammatory and contains few white cells and no crystals. Joint involvement may actually represent inflammatory periarthritis or peritendinitis and not true arthritis. T e recurrent, transient nature of the arthritis may suggest rheumatic fever, especially because patients with hyperlipoproteinemia may have an elevated erythrocyte sedimentation rate and elevated

antistreptolysin O titers (the latter being quite common). Attacks of tendinitis, including the large Achilles and patellar tendons, may come on gradually and last only a few days or may be acute as described above. Patients may be asymptomatic between attacks. Achilles tendinitis and other joint manifestations often precede the appearance of xanthomas and may be the first clinical indication of hyperlipoproteinemia. Attacks of tendinitis may follow treatment with a lipid-lowering drug. Over time, patients may develop tendinous xanthomas in the Achilles, patellar, and extensor tendons of the hands and feet. Xanthomas have also been reported in the peroneal tendon, the plantar aponeurosis, and the periosteum overlying the distal tibia. T ese xanthomas are located within tendon fibers. Tuberous xanthomas are soft subcutaneous masses located over the extensor surfaces of the elbows, knees, and hands as well as on the buttocks. T ey appear during childhood in homozygous patients and after the age of 30 in heterozygous patients. Patients with elevated plasma levels of very-low-density lipoprotein (VLDL) and triglycerides (previously referred to as type IV hyperlipoproteinemia) may also have a mild inflammatory arthritis affecting large and small peripheral joints, usually in an asymmetric pattern, with only a few joints involved at a time. T e onset of arthritis usually comes in middle age. Arthritis may be persistent or recurrent, with episodes lasting a few days or weeks. Some patients may experience severe joint pain or morning stiffness. Joint tenderness and periarticular hyperesthesia may also be present, as may synovial thickening. Joint fluid is usually noninflammatory and without crystals but may have increased white blood cell counts with predominantly mononuclear cells. Radiographs may show juxtaarticular osteopenia and cystic lesions. Large bone cysts have been noted in a few patients. Xanthoma and bone cysts are also observed in other lipoprotein disorders. T e pathogenesis of arthritis in patients with familial hypercholesterolemia or with elevated levels of VLDL and triglycerides is not well understood. NSAIDs or analgesics usually provide adequate relief of symptoms when used on an as-needed basis.

Patients may improve clinically as they are treated with lipid-lowering agents; however, patients treated with an HMG-CoA reductase inhibitor may experience myalgias, and a few patients develop myopathy, myositis, or even rhabdomyolysis. Patients who develop myositis during statin therapy may be susceptible to this adverse effect because of an underlying muscle disorder and should be reevaluated after discontinuation of the drug. Myositis has also been reported with the use of niacin **(Chap. 17)** but is less common than myalgias.

Musculoskeletal syndromes have not clearly been associated with the more common mixed hyperlipidemias seen in general practice.

OTHER ARTHRITIDES

NEUROPATHIC JOINT DISEASE

Neuropathic joint disease (Charcot joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. Normal muscular reflexes that modulate joint movement are impaired. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease **(Fig. 23-1)**. A variety of other disorders are associated with neuropathic arthritis, including tabes dorsalis, leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease has been reported in patients who have received intraarticular glucocorticoid injections, but this is a rare complication and was not observed in one series of patients with knee osteoarthritis who received intraarticular glucocorticoid injections every 3 months for 2 years. T e distribution of joint involvement depends on the underlying neurologic disorder **(Table 23-2)**. In tabes dorsalis, the knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints.

PATHOLOGY AND PATHOPHYSIOLOGY

T e pathologic changes in the neuropathic joint are similar to those found in the severe osteoarthritic joint. T ere is fragmentation and eventual loss of articular



FIGURE 23-1
Charcot arthropathy associated with diabetes mellitus. Lateral foot radiograph demonstrating complete loss of the arch due to bony fragmentation and dislocation in the midfoot. (Courtesy of Andrew Neckers, MD, and Jean Schils, MD; with permission.)

TABLE 23-2

DISORDERS ASSOCIATED WITH NEUROPATHIC JOINT DISEASE	
Diabetes mellitus	Amyloidosis
Tabes dorsalis	Leprosy
Meningomyelocele	Congenital indifference to pain
Syringomyelia	Peroneal muscular atrophy

cartilage with eburnation of the underlying bone. Osteophytes are found at the joint margins. With more advanced disease, erosions are present on the joint surface. Fractures, devitalized bone, intraarticular loose bodies, and microscopic fragments of cartilage and bone may be present.

At least two underlying mechanisms are believed to be involved in the pathogenesis of neuropathic arthritis. An abnormal autonomic nervous system is thought to be responsible for the dysregulated blood flow to the joint with subsequent resorption of bone. Loss of bone, particularly in the diabetic foot, may be the initial finding. With the loss of deep pain, proprioception, and protective neuromuscular reflexes, the joint is subjected to repeated microtrauma, resulting in ligamental tears and bone fractures. T e injury that follows frequent intraarticular glucocorticoid injections is thought to be due to the analgesic effect of glucocorticoids, leading to overuse of an already damaged joint; the result is accelerated cartilage damage, although steroid-induced cartilage damage be more common in some other animal species than in humans. It is not understood why only a few patients with neuropathy develop clinically evident neuropathic arthritis.

CLINICAL MANIFESTATIONS

Neuropathic joint disease usually begins in a single joint and then becomes apparent in other joints, depending on the underlying neurologic disorder. T e involved joint becomes progressively enlarged as a result of bony overgrowth and synovial effusion. Loose bodies may be palpated in the joint cavity. Joint instability, subluxation, and crepitus occur as the disease progresses. Neuropathic joints may develop rapidly, and a totally disorganized joint with multiple bony fragments may evolve within weeks or months. T e amount of pain experienced by the patient is less than would be anticipated from the degree of joint damage. Patients may experience sudden joint pain from intraarticular fractures of osteophytes or condyles.

Neuropathic arthritis is encountered most often in patients with diabetes mellitus, with an incidence of ~0.5%. T e onset of disease usually comes at an age of ≥50 years in a patient who has had diabetes for several years, but exceptions occur. T e tarsal and tarsometatarsal joints are most often affected, with the metatarsophalangeal and talotibial joints next most commonly involved. T e knees and spine are occasionally involved. Patients often attribute the onset of foot pain to antecedent trauma such as twisting of the foot. Neuropathic changes may develop rapidly after a foot fracture or dislocation. T e foot and ankle are often swollen. Downward collapse of the tarsal bones leads to convexity of the sole, referred to as a "rocker foot." Large osteophytes may protrude from the top of the foot. Calluses frequently form over the metatarsal heads and may lead to infected ulcers and osteomyelitis. T e value of protective inserts and orthotics, as well as regular foot examination, cannot be overstated. Radiographs may show resorption and tapering of the distal metatarsal bones. T e term Lisfranc fracture-dislocation is sometimes used to describe the destructive changes at the tarsometatarsal joints.

DIAGNOSIS

T e diagnosis of neuropathic arthritis is based on the clinical features and characteristic radiographic findings in a patient with underlying sensory neuropathy. T e differential diagnosis of neuropathic arthritis depends upon the severity of the process and includes osteomyelitis, avascular necrosis, advanced osteoarthritis, stress fractures, and calcium pyrophosphate deposition disease. Radiographs in neuropathic arthritis initially show changes of osteoarthritis with joint space narrowing, subchondral bone sclerosis, osteophytes, and joint effusions; marked destructive and hypertrophic changes follow later. T e radiographic findings of neuropathic arthritis may be dif cult to differentiate from those of osteomyelitis, especially in the diabetic foot. T e joint margins in a neuropathic joint tend to be distinct, while in osteomyelitis they are blurred. Imaging studies may be helpful, but cultures of tissue from the joint are often required to exclude osteomyelitis. MRI and bone scans using indium 111–labeled white blood cells or indium 111–labeled immunoglobulin G, which will show increased uptake in osteomyelitis but not in a neuropathic joint, may be useful. A technetium bone scan will not distinguish osteomyelitis from neuropathic arthritis, as increased uptake is observed in both. T e joint fluid in neuropathic arthritis is noninflammatory; may be xanthochromic or even bloody; and may contain fragments of synovium, cartilage, and bone. T e finding of calcium pyrophosphate dihydrate crystals supports the diagnosis of crystal-associated arthropathy. In the absence of such crystals, an increased number of leukocytes may indicate osteomyelitis.

TREATMENT Neuropathic Joint Disease

The primary focus of treatment is to stabilize the joint. Treatment of the underlying disorder, even if successful, does not usually affect established joint disease. Braces and splints are helpful. Their use requires close surveillance, because patients may be unable to appreciate pressure from a poorly adjusted brace. In the diabetic patient, early recognition of Charcot foot and its treatment—prohibition of weight bearing by the foot for at least 8 weeks—may possibly prevent severe disease from developing. Fusion of an unstable joint may improve function and reduce pain, but nonunion is frequent, especially when immobilization of the joint is inadequate.

HYPERTROPHIC OSTEOARTHROPATHY AND CLUBBING

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of digits and, in more advanced stages, by periosteal new-bone formation and synovial effusions. HOA may be primary or familial and may begin in childhood. Secondary HOA is associated with intrathoracic malignancies, suppurative and some hypoxemic lung diseases, congenital heart disease, and a variety of other disorders. Clubbing is almost always a feature of HOA but can occur as an isolated manifestation **(Fig. 23-2)**. The presence of clubbing in isolation may be congenital or represent either an early stage or one element in the spectrum of HOA. Isolated acquired clubbing has the same clinical significance as clubbing associated with periostitis.

Pathology and pathophysiology of acquired HOA

In HOA, bone changes in the distal extremities begin as periostitis followed by new bone formation. At this stage, a radiolucent area may be observed between the new periosteal bone and the subjacent cortex. As the process progresses, multiple layers of new bone are deposited and become contiguous with the cortex, with consequent cortical thickening. The outer portion of the bone is laminated in appearance, with an irregular surface. Initially, the process of periosteal new-bone formation involves the proximal and distal diaphyses of the tibia, fibula, radius, and ulna and, less frequently, the femur, humerus, metacarpals, metatarsals, and phalanges. Occasionally, scapulae, clavicles, ribs, and pelvic bones are also affected. The adjacent interosseous membranes may become ossified. The distribution of bone manifestations is usually bilateral and symmetric. The soft tissue overlying the distal third of the arms and legs may be thickened. Proliferation of connective tissue occurs in the nail bed and volar pad of digits, giving the distal phalanges a clubbed appearance. Small blood vessels in the clubbed digits are dilated and have thickened walls. In addition, the number of arteriovenous anastomoses is increased.

Several theories have been suggested for the pathogenesis of HOA, but many have been disproved or have not explained the condition's development in all clinical disorders with which it is associated. Previously proposed neurogenic and humoral theories are no longer considered likely explanations for HOA. Studies have suggested a role for platelets in the development of HOA. It has been observed that megakaryocytes and large platelet particles present in the venous circulation are fragmented in their passage through normal lung. In patients with cyanotic congenital heart disease and in other disorders associated with right-to-left shunts, these large platelet particles bypass the lung and reach the distal extremities, where they can interact with endothelial cells. Platelet–endothelial cell activation in the distal portion of the extremities may result in the release of platelet-derived growth factor (PDGF) and other factors leading to the proliferation of connective tissue and periosteum. Stimulation of fibroblasts by PDGF and transforming growth factor β results in cell growth and collagen synthesis. Elevated plasma levels of von Willebrand factor antigen have been found in patients with both primary and secondary forms of HOA, indicating endothelial activation or damage. Abnormalities of collagen synthesis have been demonstrated in the involved skin of patients with primary HOA. Other factors are undoubtedly involved in the pathogenesis of HOA, and further studies are needed to elucidate this disorder.



FIGURE 23-2
Clubbing of the fingers. (Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, © 1991, 1995. Used by permission of the American College of Rheumatology.)

Clinical manifestations

Primary or familial HOA, also referred to as pachydermoperiostitis or Touraine-Solente-Golé syndrome,

usually begins insidiously at puberty. In a smaller proportion of patients, the onset comes in the first year of life. T e disorder is inherited as an autosomal dominant trait with variable expression and is nine times more common among boys than among girls. Approximately one-third of patients have a family history of primary HOA.

Primary HOA is characterized by clubbing, periostitis, and unusual skin features. A small number of patients with this syndrome do not express clubbing. T e skin changes and periostitis are prominent features of this syndrome. T e skin becomes thickened and coarse. Deep nasolabial folds develop, and the forehead may become furrowed. Patients may have heavy-appearing eyelids and ptosis. T e skin is often greasy, and there may be excessive sweating of the hands and feet. Patients may also experience acne vulgaris, seborrhea, and folliculitis. In a few patients, the skin over the scalp becomes very thick and corrugated, a feature that has been descriptively termed cutis verticis gyrata. T e distal extremities, particularly the legs, become thickened as a consequence of the proliferation of new bone and soft tissue; when the process is extensive, the distal lower extremities resemble those of an elephant. T e periostitis usually is not painful, which it can be in secondary HOA. Clubbing of the fingers may be extensive, producing large, bulbous deformities and clumsiness. Clubbing also affects the toes. Patients may experience articular and periarticular pain, especially in the ankles and knees, and joint motion may be mildly restricted by periarticular bone overgrowth. Noninflammatory effusions occur in the wrists, knees, and ankles. Synovial hypertrophy is not found. Associated abnormalities observed in patients with primary HOA include hypertrophic gastropathy, bone marrow failure, female escutcheon, gynecomastia, and cranial suture defects. In patients with primary HOA, the symptoms disappear when adulthood is reached.

HOA secondary to an underlying disease occurs more frequently than primary HOA. It accompanies a variety of disorders and may precede clinical features of the associated disorder by months. Clubbing is more frequent than the full syndrome of HOA in patients with associated illnesses. Because clubbing evolves over months and is usually asymptomatic, it is often recognized first by the physician and not the patient. Patients may experience a burning sensation in their fingertips. Clubbing is characterized by widening of the fingertips, enlargement of the distal volar pad, convexity of the nail contour, and the loss of the normal 15° angle between the proximal nail and cuticle. T e thickness of the digit at the base of the nail is greater than the thickness at the distal interphalangeal joint. An objective measurement of finger clubbing can be made by determining the diameter at the base of the nail and at the distal interphalangeal joint of all 10 digits. Clubbing is present when the sum of the individual digit ratios is >10. At the bedside, clubbing can be appreciated by having the patient place the dorsal surface of the distal phalanges of the fourth fingers together with the nails opposing each other. Normally, an open area is visible between the bases of the opposing fingernails; when clubbing is present, this open space is no longer visible. T e base of the nail feels spongy when compressed, and the nail can be easily rocked on its bed. When clubbing is advanced, the finger may have a drumstick appearance, and the distal interphalangeal joint can be hyperextended. Periosteal involvement in the distal extremities may produce a burning or deep-seated aching pain. T e pain, which can be quite incapacitating, is aggravated by dependency and relieved by elevation of the affected limbs. Pressure applied over the distal forearms and legs or gentle percussion of distal long bones like the tibia may be quite painful.

Patients may experience joint pain, most often in the ankles, wrists, and knees. Joint effusions may be present; usually, they are small and noninflammatory. T e small joints of the hands are rarely affected. Severe joint or long bone pain may be the presenting symptom of an underlying lung malignancy and may precede the appearance of clubbing. In addition, the progression of HOA tends to be more rapid when associated with malignancies, most notably bronchogenic carcinoma. Noninflammatory but variably painful knee effusions may occur prior to the appearance of clubbing and symptoms of distal periostitis. Unlike primary HOA, secondary HOA does not commonly include excessive sweating and oiliness of the skin or thickening of the facial skin.

HOA occurs in 5–10% of patients with intrathoracic malignancies, the most common being bronchogenic carcinoma and pleural tumors **(Table 23-3)**. Lung metastases infrequently cause HOA. HOA is also seen in patients with intrathoracic infections, including lung abscesses, empyema, and bronchiectasis, but is uncommon in pulmonary tuberculosis. HOA may accompany chronic interstitial pneumonitis, sarcoidosis, and cystic fibrosis. In cystic fibrosis, clubbing is more common than the full syndrome of HOA. Other causes of clubbing include congenital heart disease with right-to-left shunts, bacterial endocarditis, Crohn's disease, ulcerative colitis, sprue, and neoplasms of the esophagus, liver, and small and large bowel. In patients who have congenital heart disease with right-to-left shunts, clubbing alone occurs more often than the full syndrome of HOA.

Unilateral clubbing has been found in association with aneurysms of major extremity arteries, with infected arterial grafts, and with arteriovenous fistulas of brachial vessels. Clubbing of the toes but not the

TABLE 23-3

DISORDERS ASSOCIATED WITH HYPERTROPHIC OSTEOARTHROPATHY

Pulmonary
Bronchogenic carcinoma and other neoplasms
Lung abscesses, empyema, bronchiectasis
Chronic interstitial pneumonitis
Cystic fibrosis
Sarcoidosis
Gastrointestinal
Inflammatory bowel disease
Sprue
Neoplasms: esophagus, liver, bowel
Cardiovascular
Cyanotic congenital heart disease
Subacute bacterial endocarditis
Infected arterial grafts[a]
Aortic aneurysm[b]
Aneurysm of major extremity artery[a]
Patent ductus arteriosus[b]
Arteriovenous fistula of major extremity vessel[a]
Thyroid (thyroid acropachy)
Hyperthyroidism (Graves' disease)

[a]Unilateral involvement.
[b]Bilateral lower-extremity involvement.

fingers has been associated with an infected abdominal aortic aneurysm and patent ductus arteriosus. Clubbing of a single digit may follow trauma and has been reported in tophaceous gout and sarcoidosis. While clubbing occurs more commonly than the full syndrome in most diseases, periostitis in the absence of clubbing has been observed in the affected limb of patients with infected arterial grafts.

Hyperthyroidism (Graves' disease), treated or untreated, is occasionally associated with clubbing and periostitis of the bones of the hands and feet. This condition is referred to as thyroid acropachy. Periostitis may be asymptomatic and occurs in the midshaft and diaphyseal portion of the metacarpal and phalangeal bones. Significant hand-joint pain may occur; this pain may respond to successful therapy for thyroid dysfunction. The long bones of the extremities are seldom affected. Elevated levels of long-acting thyroid stimulator are found in the sera of these patients.

Laboratory Findings

The laboratory abnormalities reflect the underlying disorder. The synovial fluid of involved joints has <500 white cells/μL, and the cells are predominantly mononuclear. Radiographs show a faint radiolucent line beneath the new periosteal bone along the shaft of long bones at their distal end. These changes are observed most frequently at the ankles, wrists, and knees. The ends of the distal phalanges may show osseous resorption. Radionuclide studies show pericortical linear uptake along the cortical margins of long bones that may precede any radiographic changes.

TREATMENT Hypertrophic Osteoarthropathy

The treatment of HOA aims to identify the associated disorder and treat it appropriately. The symptoms and signs of HOA may disappear completely with removal of or effective chemotherapy for a tumor or with antibiotic therapy for a chronic pulmonary infection and drainage of the infected site. Vagotomy or percutaneous block of the vagus nerve leads to symptomatic relief in some patients. NSAIDs or analgesics may help control symptoms of HOA.

REFLEX SYMPATHETIC DYSTROPHY SYNDROME

The reflex sympathetic dystrophy syndrome is now referred to as complex regional pain syndrome, type 1, according to the new classification system of the International Association for the Study of Pain. This syndrome is characterized by pain and swelling, usually of a distal extremity, accompanied by vasomotor instability, trophic skin changes, and the rapid development of bony demineralization.

TIETZE SYNDROME AND COSTOCHONDRITIS

Tietze syndrome is manifested by painful swelling of one or more costochondral articulations. The age of onset is usually before 40, and both sexes are affected equally. In most patients, only one joint is involved, usually the second or third costochondral joint. The onset of anterior chest pain may be sudden or gradual. The pain may radiate to the arms or shoulders and is aggravated by sneezing, coughing, deep inspirations, or twisting motions of the chest. The term costochondritis is often used interchangeably with *T*ietze syndrome, but some workers restrict the former term to pain of the costochondral articulations without swelling. Costochondritis is observed in patients over age 40; tends to affect the third, fourth, and fifth costochondral joints; and occurs more often in women. Both syndromes may mimic cardiac or upper abdominal causes of pain. Rheumatoid arthritis, ankylosing spondylitis, and reactive arthritis may involve costochondral joints but are distinguished easily by their other clinical features. Other skeletal causes of anterior chest wall pain are xiphoidalgia and the slipping rib syndrome, which usually involves the tenth rib. Malignancies such as

breast cancer, prostate cancer, plasma cell cytoma, and sarcoma can invade the ribs, thoracic spine, or chest wall and produce symptoms suggesting Tietze syndrome. Patients with osteomalacia may have significant rib pain, with or without documented microfractures. T ese conditions should be distinguishable by radiography, bone scanning, vitamin D measurement, or biopsy. Analgesics, anti-inflammatory drugs, and local glucocorticoid injections usually relieve symptoms of costochondritis/Tietze syndrome. Care should be taken to avoid overdiagnosing these syndromes in patients with acute chest pain syndromes; many patients will be tender to overly vigorous palpation of the costochondral joints.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome is characterized by multiple areas of localized musculoskeletal pain and tenderness in association with tender points. T e pain is deep and aching and may be accompanied by a burning sensation. Myofascial pain may be regional and follow trauma, overuse, or prolonged static contraction of a muscle or muscle group, which may occur when an individual is reading or writing at a desk or working at a computer. In addition, this syndrome may be associated with underlying osteoarthritis of the neck or low back. Pain may be referred from tender points to defined areas distant from the area of original tenderness. Palpation of the tender point reproduces or accentuates the pain. T e tender points are usually located in the center of a muscle belly, but they can occur at other sites such as costosternal junctions, the xiphoid process, ligamentous and tendinous insertions, fascia, and fatty areas. Tender point sites in muscle have been described as feeling indurated and taut, and palpation may cause the muscle to twitch. T ese findings, however, have been shown not to be unique to myofascial pain syndrome: in a controlled study, they were also present in some "normal" subjects. Myofascial pain most often involves the posterior neck, low back, shoulders, and chest. Chronic pain in the muscles of the posterior neck may involve referral of pain from a tender point in the erector neck muscle or upper trapezius to the head, leading to persistent headaches that may last for days. Tender points in the paraspinal muscles of the low back may refer pain to the buttock. Pain may be referred down the leg from a tender point in the gluteus medius and can mimic sciatica. A tender point in the infraspinatus muscle may produce local and referred pain over the lateral deltoid and down the outside of the arm into the hand. Injection of a local anesthetic such as 1% lidocaine into the tender point site often results in at least transient pain relief. Another useful technique is first to spray an agent such as ethyl chloride from the tender point toward the area of referred pain and then to stretch the muscle. T is maneuver may need to be repeated several times. Massage and application of ultrasound to the affected area also may be beneficial. Patients should be instructed in methods to prevent muscle stresses related to work and recreation. Posture and resting positions are important in preventing muscle tension. T e prognosis in most patients is good. In some patients, regionally localized myofascial pain syndrome may seem to evolve into more generalized fibromyalgia **(Chap. 22)**. Abnormal or nonrestorative sleep is a common accompaniment in these patients and may need to be specifically addressed.

NEOPLASIAS AND ARTHRITIS

Primary tumors and tumor-like disorders of synovium are uncommon but should be considered in the differential diagnosis of monarticular joint disease. In addition, metastases to bone and primary bone tumors adjacent to a joint may produce joint symptoms.

Pigmented villonodular synovitis (PVNS) is characterized by the slowly progressive, exuberant, benign proliferation of synovial tissue, usually involving a single joint. T e most common age of onset is in the third decade, and women are affected slightly more often than men. T e cause of this disorder is unknown.

T e synovium has a brownish color and numerous large, fingerlike villi that fuse to form pedunculated nodules. T ere is marked hyperplasia of synovial cells in the stroma of the villi. Hemosiderin granules and lipids are found in the cytoplasm of macrophages and in the interstitial tissue. Multinucleated giant cells may be present. T e proliferative synovium grows into the subsynovial tissue and invades adjacent cartilage and bone.

T e clinical picture of PVNS is characterized by the insidious onset of persistent swelling and pain in affected joints, most commonly the knee. Other joints affected include the hips, ankles, calcaneocuboid joints, elbows, and small joints of the fingers or toes. T e disease may also involve the common flexor sheath of the hands or fingers. Less often, tendon sheaths in the wrist, ankle, or foot may be involved. Symptoms of pain, a catching sensation, or stiffness may initially be mild and intermittent and may be present for years before the patient seeks medical attention. Radiographs may show joint space narrowing, erosions, and subchondral cysts. T e diagnosis of PVNS is strongly suggested by gradient echo MRI, which reveals a synovial mass lesion of low signal intensity typical of tissue containing hemosiderin **(Fig. 23-3)**. T e joint fluid contains blood and



FIGURE 23-3
Pigmented villonodular synovitis. MRI gradient echo sagittal image showing a mass that abuts the neck of the talus with marked low signal typical of tissue containing hemosiderin. (Courtesy of Donald Flemming, MD; with permission.)

is dark red or almost black in color. Lipid-containing macrophages may be present in the fluid. The joint fluid may be clear if hemorrhage has not occurred. Some patients have polyarticular involvement.

The treatment for PVNS is complete synovectomy. With incomplete synovectomy, the villonodular synovitis recurs, and the rate of tissue growth may be faster than it was originally. Irradiation of the involved joint has been successful in some patients.

Synovial chondromatosis is a disorder characterized by multiple focal metaplastic growths of normal-appearing cartilage in the synovium or tendon sheath. Segments of cartilage break loose and continue to grow as loose bodies. When calcification and ossification of loose bodies occur, the disorder is referred to as synovial osteochondromatosis. The disorder is usually monarticular and affects young to middle-aged individuals. The knee is most often involved, followed by hip, elbow, and shoulder. Symptoms are pain, swelling, and decreased motion of the joint. Radiographs may show several rounded calcifications within the joint cavity. Treatment is synovectomy; however, as in PVNS, the tumor may recur.

Synovial sarcoma is a malignant neoplasm often found near a large joint of both upper and lower extremities, being more common in the lower extremity. It seldom arises within the joint itself. Synovial sarcomas constitute 10% of soft tissue sarcomas. The tumor is believed to arise from primitive mesenchymal tissue that differentiates into epithelial cells and/or spindle cells. Small foci of calcification may be present in the tumor mass. Synovial sarcoma occurs most often in young adults and is more common in men. The tumor presents as a slowly growing deep-seated mass near a joint, without much pain. The area of the knee is the most common site, followed by the foot, ankle, elbow, and shoulder. Other primary sites include the buttocks, abdominal wall, retroperitoneum, and mediastinum. The tumor spreads along tissue planes. The most common site of visceral metastasis is the lung. The diagnosis is made by biopsy. Treatment consists of wide resection of the tumor, including adjacent muscle and regional lymph nodes, followed by chemotherapy and radiation therapy. Amputation of the involved distal extremity may be required. Chemotherapy may be beneficial in some patients with metastatic disease. Isolated sites of pulmonary metastasis can be surgically removed. The 5-year survival rate with treatment is variable and depends on the staging of the tumor, ranging from ~25% to ≥60%. Synovial sarcomas tend to recur locally and metastasize to regional lymph nodes, lungs, and skeleton.

In addition to the rare direct metastases of solid cell tumors to the highly vascular synovium, neoplasia arising from nonarticular organ sites can affect joints in other ways. Acute leukemias in children can mimic juvenile inflammatory arthritis with severe joint pain and fever. In adults, chronic and acute myeloid leukemia can infiltrate the synovium in rare instances. The rarely occurring hairy cell leukemia has a peculiar tendency to cause episodic inflammatory oligoarthritis and tenosynovitis; these episodes are dramatic and mimic acute gout attacks. They respond to potent anti-inflammatory therapy with glucocorticoids; with remission of the leukemia, they may abate. Carcinomas can be associated with several paraneoplastic articular syndromes, including HOA (discussed above). Acute palmar fasciitis with polyarthritis is a well-described but rare condition associated with certain cancers, mainly adenocarcinomas. Clinically, this syndrome is fairly abrupt in onset, with pain in the metacarpophalangeal and proximal interphalangeal joints of the hands and rapidly evolving contractures of the fingers due to thickening of the palmar (flexor) tendons. A similar syndrome can be seen in diabetics. Paraneoplastic arthritis has been described and may occur in several patterns: asymmetric disease predominantly affecting the lower extremity joints and symmetric polyarthritis with hand joint involvement. Tumors are often found after the onset of the arthritis, and many patients have a preceding period of malaise or weight loss. The onset is often acute, and patients tend to be older men. These features should raise the specter of an underlying malignancy (or a viral infection such as hepatitis C) as the cause of the arthritis. In one series, the symptoms resolved with successful therapy for

the malignancy and did not recur with relapse of the malignancy. Dermatomyositis has a well-described association with neoplasms and may include joint pain and arthritis. Malignancy-associated arthritis may be responsive to NSAIDs and to treatment of the primary neoplasm.

Acknowledgment

T is chapter represents a revised version of the chapter authored by Dr. Bruce C. Gilliland that appeared in previous editions of Harrison's. Dr. Gilliland passed away on February 17, 2007. He had been a contributor to Harrison's Principles of Internal Medicine since the 11th edition.

CHAPTER 24

PERIARTICULAR DISORDERS OF THE EXTREMITIES

Carol A. Langford

A number of periarticular disorders have become increasingly common, due in part to greater participation in recreational sports by individuals of a wide range of ages. Periarticular disorders most commonly affect the knee or shoulder. With the exception of bursitis, hip pain is most often articular or is being referred from disease affecting another structure **(Chap. 18)**. T is chapter discusses some of the more common periarticular disorders.

BURSITIS

Bursitis is inflammation of a bursa, which is a thin-walled sac lined with synovial tissue. T e function of the bursa is to facilitate movement of tendons and muscles over bony prominences. Excessive frictional forces from overuse, trauma, systemic disease (e.g., rheumatoid arthritis, gout), or infection may cause bursitis. Subacromial bursitis (subdeltoid bursitis) is the most common form of bursitis. T e subacromial bursa, which is contiguous with the subdeltoid bursa, is located between the undersurface of the acromion and the humeral head and is covered by the deltoid muscle. Bursitis is caused by repetitive overhead motion and often accompanies rotator cuff tendinitis. Another frequently encountered form is trochanteric bursitis, which involves the bursa around the insertion of the gluteus medius onto the greater trochanter of the femur. Patients experience pain over the lateral aspect of the hip and upper thigh and have tenderness over the posterior aspect of the greater trochanter. External rotation and resisted abduction of the hip elicit pain. Olecranon bursitis occurs over the posterior elbow, and when the area is acutely inflamed, infection or gout should be excluded by aspirating the bursa and performing a Gram stain and culture on the fluid as well as examining the fluid for urate crystals. Achilles bursitis involves the bursa located above the insertion of the tendon to the calcaneus and results from overuse and wearing tight shoes. Retrocalcaneal bursitis involves the bursa that is located between the calcaneus and posterior surface of the Achilles tendon. T e pain is experienced at the back of the heel, and swelling appears on the medial and/or lateral side of the tendon. It occurs in association with spondyloarthritides, rheumatoid arthritis, gout, or trauma. Ischial bursitis affects the bursa separating the gluteus medius from the ischial tuberosity and develops from prolonged sitting and pivoting on hard surfaces. Iliopsoas bursitis affects the bursa that lies between the iliopsoas muscle and hip joint and is lateral to the femoral vessels. Pain is experienced over this area and is made worse by hip extension and flexion. Anserine bursitis is an inflammation of the sartorius bursa located over the medial side of the tibia just below the knee and under the conjoint tendon and is manifested by pain on climbing stairs. Tenderness is present over the insertion of the conjoint tendon of the sartorius, gracilis, and semitendinosus. Prepatellar bursitis occurs in the bursa situated between the patella and overlying skin and is caused by kneeling on hard surfaces. Gout or infection may also occur at this site. Bursitis is typically diagnosed by history and physical examination, but visualization by ultrasound may play a useful role in selected instances for diagnosis and directed guidance of glucocorticoid injection. Treatment of bursitis consists of prevention of the aggravating situation, rest of the involved part, administration of a nonsteroidal anti-inflammatory drug (NSAID) where appropriate for an individual patient, or local glucocorticoid injection.

ROTATOR CUFF TENDINITIS AND IMPINGEMENT SYNDROME

Tendinitis of the rotator cuff is the major cause of a painful shoulder and is currently thought to be caused by

inflammation of the tendon(s). T e rotator cuff consists of the tendons of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles, and inserts on the humeral tuberosities. Of the tendons forming the rotator cuff, the supraspinatus tendon is the most often affected, probably because of its repeated impingement (impingement syndrome) between the humeral head and the undersurface of the anterior third of the acromion and coracoacromial ligament above as well as the reduction in its blood supply that occurs with abduction of the arm **(Fig. 24-1)**. T e tendon of the infraspinatus and that of the long head of the biceps are less commonly involved. T e process begins with edema and hemorrhage of the rotator cuff, which evolves to fibrotic thickening and eventually to rotator cuff degeneration with tendon tears and bone spurs. Subacromial bursitis also accompanies this syndrome. Symptoms usually appear after injury or overuse, especially with activities involving elevation of the arm with some degree of forward flexion. Impingement syndrome occurs in persons participating in baseball, tennis, swimming, or occupations that require repeated elevation of the arm. T ose over age 40 are particularly susceptible. Patients complain of a dull aching in the shoulder, which may interfere with sleep. Severe pain is experienced when the arm is actively abducted into an overhead position. T e arc between 60° and 120° is especially painful. Tenderness is present over the lateral aspect of the humeral head just below the acromion. NSAIDs, local glucocorticoid injection, and physical therapy may relieve symptoms. Surgical decompression of the subacromial space may be necessary in patients refractory to conservative treatment.

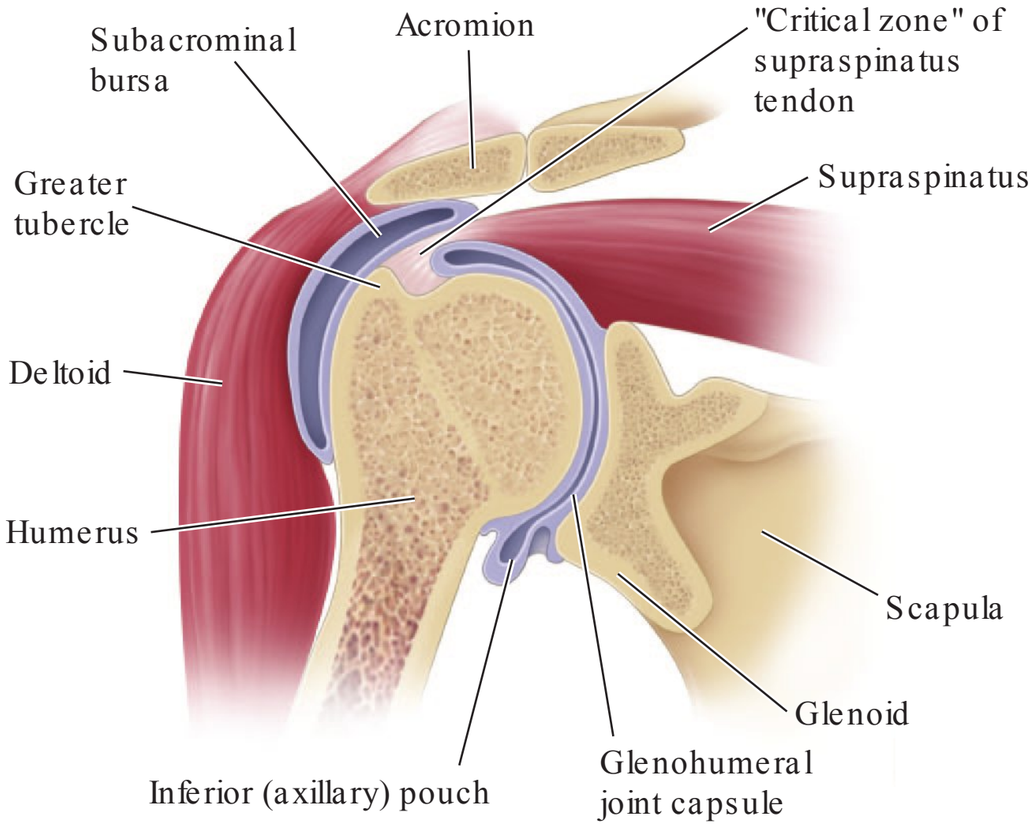


FIGURE 24-1
Coronal section of the shoulder illustrating the relationships of the glenohumeral joint, the joint capsule, the subacromial bursa, and the rotator cuf (supraspinatus tendon). (From F Kozin, in Arthritis and Allied Conditions, 13th ed, WJ Koopman [ed]. Baltimore, Williams &Wilkins, 1997, with permission.)

Patients may tear the supraspinatus tendon acutely by falling on an outstretched arm or lifting a heavy object. Symptoms are pain along with weakness of abduction and external rotation of the shoulder. Atrophy of the supraspinatus muscles develops. T e diagnosis is established by arthrogram, ultrasound, or magnetic resonance imaging (MRI). Surgical repair may be necessary in patients who fail to respond to conservative measures. In patients with moderate-to-severe tears and functional loss, surgery is indicated.

CALCIFIC TENDINITIS

T is condition is characterized by deposition of calcium salts, primarily hydroxyapatite, within a tendon. T e exact mechanism of calcification is not known but may be initiated by ischemia or degeneration of the tendon. T e supraspinatus tendon is most often affected because it is frequently impinged on and has a reduced blood supply when the arm is abducted. T e condition usually develops after age 40. Calcification within the tendon may evoke acute inflammation, producing sudden and severe pain in the shoulder. However, it may be asymptomatic or not related to the patient's symptoms. Diagnosis of calcific tendonitis can be made by ultrasound or radiograph. Most cases are self-limited and respond to conservative therapy with physical therapy and/or NSAIDs. A subset of patients is refractory and requires ultrasound-guided percutaneous needle aspiration and lavage or surgery.

BICIPITAL TENDINITIS AND RUPTURE

Bicipital tendinitis, or tenosynovitis, is produced by friction on the tendon of the long head of the biceps as it passes through the bicipital groove. When the inflammation is acute, patients experience anterior shoulder pain that radiates down the biceps into the forearm. Abduction and external rotation of the arm are painful and limited. T e bicipital groove is very tender to palpation. Pain may be elicited along the course of the tendon by resisting supination of the forearm with the elbow at 90° (Yergason's supination sign). Acute rupture of the tendon may occur with vigorous exercise of the arm and is often painful. In a young patient, it should be repaired surgically. Rupture of the tendon in an older person may be associated with little or no pain and is recognized by the presence of persistent swelling of the biceps produced by the retraction of the long head of the biceps. Surgery is usually not necessary in this setting.

DE QUERVAIN'S TENOSYNOVITIS

In this condition, inflammation involves the abductor pollicis longus and the extensor pollicis brevis as these

tendons pass through a fibrous sheath at the radial styloid process. The usual cause is repetitive twisting of the wrist. It may occur in pregnancy, and it also occurs in mothers who hold their babies with the thumb outstretched. Patients experience pain on grasping with their thumb, such as with pinching. Swelling and tenderness are often present over the radial styloid process. The Finkelstein sign is positive, which is elicited by having the patient place the thumb in the palm and close the fingers over it. The wrist is then ulnarly deviated, resulting in pain over the involved tendon sheath in the area of the radial styloid. Treatment consists initially of splinting the wrist and an NSAID. When severe or refractory to conservative treatment, glucocorticoid injections can be very effective.

PATELLAR TENDINITIS (JUMPER'S KNEE)

Tendinitis involves the patellar tendon at its attachment to the lower pole of the patella. Patients may experience pain when jumping during basketball or volleyball, going up stairs, or doing deep knee squats. Tenderness is noted on examination over the lower pole of the patella. Treatment consists of rest, icing, and NSAIDs, followed by strengthening and increasing flexibility.

ILIOTIBIAL BAND SYNDROME

The iliotibial band is a thick connective tissue that runs from the ilium to the fibula. Patients with iliotibial band syndrome most commonly present with aching or burning pain at the site where the band courses over the lateral femoral condyle of the knee; pain may also radiate up the thigh, toward the hip. Predisposing factors for iliotibial band syndrome include a varus alignment of the knee, excessive running distance, poorly fitted shoes, or continuous running on uneven terrain. Treatment consists of rest, NSAIDs, physical therapy, and addressing risk factors such as shoes and running surface. Glucocorticoid injection into the area of tenderness can provide relief, but running must be avoided for at least 2 weeks after the injection. Surgical release of the iliotibial band has been helpful in rare patients for whom conservative treatment has failed.

ADHESIVE CAPSULITIS

Often referred to as "frozen shoulder," adhesive capsulitis is characterized by pain and restricted movement of the shoulder, usually in the absence of intrinsic shoulder disease. Adhesive capsulitis may follow bursitis or tendinitis of the shoulder or be associated with systemic disorders such as chronic pulmonary disease, myocardial infarction, and diabetes mellitus. Prolonged immobility of the arm contributes to the development of adhesive capsulitis. Pathologically, the capsule of the shoulder is thickened, and a mild chronic inflammatory infiltrate and fibrosis may be present.

Adhesive capsulitis occurs more commonly in women after age 50. Pain and stiffness usually develop gradually but progress rapidly in some patients. Night pain is often present in the affected shoulder, and pain may interfere with sleep. The shoulder is tender to palpation, and both active and passive movement are restricted. Radiographs of the shoulder show osteopenia. The diagnosis is typically made by physical examination but can be confirmed if necessary by arthrography, in that only a limited amount of contrast material, usually <15 mL, can be injected under pressure into the shoulder joint.

In most patients, the condition improves spontaneously 1–3 years after onset. While pain usually improves, many patients are left with some limitation of shoulder motion. Early mobilization of the arm following an injury to the shoulder may prevent the development of this disease. Physical therapy provides the foundation of treatment for adhesive capsulitis. Local injections of glucocorticoids and NSAIDs may also provide relief of symptoms. Slow but forceful injection of contrast material into the joint may lyse adhesions and stretch the capsule, resulting in improvement of shoulder motion. Manipulation under anesthesia may be helpful in some patients.

LATERAL EPICONDYLITIS (TENNIS ELBOW)

Lateral epicondylitis, or tennis elbow, is a painful condition involving the soft tissue over the lateral aspect of the elbow. The pain originates at or near the site of attachment of the common extensors to the lateral epicondyle and may radiate into the forearm and dorsum of the wrist. The pain usually appears after work or recreational activities involving repeated motions of wrist extension and supination against resistance. Most patients with this disorder injure themselves in activities other than tennis, such as pulling weeds, carrying suitcases or briefcases, or using a screwdriver. The injury in tennis usually occurs when hitting a backhand with the elbow flexed. Shaking hands and opening doors can reproduce the pain. Striking the lateral elbow against a solid object may also induce pain.

The treatment is usually rest along with administration of an NSAID. Ultrasound, icing, and friction massage may also help relieve pain. When pain is severe, the elbow is placed in a sling or splinted at 90° of flexion. When the pain is acute and well localized, injection of a glucocorticoid using a small-gauge needle may be effective. Following injection, the patient should be advised to rest the arm for at least 1 month and avoid activities that would aggravate the elbow. Once symptoms have subsided, the patient should begin

rehabilitation to strengthen and increase flexibility of the extensor muscles before resuming physical activity involving the arm. A forearm band placed 2.5–5.0 cm (1–2 in.) below the elbow may help to reduce tension on the extensor muscles at their attachment to the lateral epicondyle. T e patient should be advised to restrict activities requiring forcible extension and supination of the wrist. Improvement may take several months. T e patient may continue to experience mild pain but, with care, can usually avoid the return of debilitating pain. Occasionally, surgical release of the extensor aponeurosis may be necessary.

MEDIAL EPICONDYLITIS

Medial epicondylitis is an overuse syndrome resulting in pain over the medial side of the elbow with radiation into the forearm. T e cause of this syndrome is considered to be repetitive resisted motions of wrist flexion and pronation, which lead to microtears and granulation tissue at the origin of the pronator teres and forearm flexors, particularly the flexor carpi radialis. T is overuse syndrome is usually seen in patients >35 years and is much less common than lateral epicondylitis. It occurs most often in work-related repetitive activities but also occurs with recreational activities such as swinging a golf club or throwing a baseball. On physical examination, there is tenderness just distal to the medial epicondyle over the origin of the forearm flexors. Pain can be reproduced by resisting wrist flexion and pronation with the elbow extended. Radiographs are usually normal. T e differential diagnosis of patients with medial elbow symptoms includes tears of the pronator teres, acute medial collateral ligament tear, and medial collateral ligament instability. Ulnar neuritis has been found in 25–50% of patients with medial epicondylitis and is associated with tenderness over the ulnar nerve at the elbow as well as hypesthesia and paresthesia on the ulnar side of the hand.

T e initial treatment of medial epicondylitis is conservative, involving rest, NSAIDs, friction massage, ultrasound, and icing. Some patients may require splinting. Injections of glucocorticoids at the painful site may also be effective. Patients should be instructed to rest for at least 1 month. Also, patients should start physical therapy once the pain has subsided. In patients with chronic debilitating medial epicondylitis that remains unresponsive after at least a year of treatment, surgical release of the flexor muscle at its origin may be necessary and is often successful.

PLANTAR FASCIITIS

Plantar fasciitis is a common cause of foot pain in adults, with the peak incidence occurring in people between the ages of 40 and 60 years. T e pain originates at or near the site of the plantar fascia attachment to the medial tuberosity of the calcaneus. Several factors that increase the risk of developing plantar fasciitis include obesity, pes planus (flat foot or absence of the foot arch when standing), pes cavus (high-arched foot), limited dorsiflexion of the ankle, prolonged standing, walking on hard surfaces, and faulty shoes. In runners, excessive running and a change to a harder running surface may precipitate plantar fasciitis.

T e diagnosis of plantar fasciitis can usually be made on the basis of history and physical examination alone. Patients experience severe pain with the first steps on arising in the morning or following inactivity during the day. T e pain usually lessens with weight-bearing activity during the day, only to worsen with continued activity. Pain is made worse on walking barefoot or up stairs. On examination, maximal tenderness is elicited on palpation over the inferior heel corresponding to the site of attachment of the plantar fascia.

Imaging studies may be indicated when the diagnosis is not clear. Plain radiographs may show heel spurs, which are of little diagnostic significance. Ultrasonography in plantar fasciitis can demonstrate thickening of the fascia and diffuse hypoechogenicity, indicating edema at the attachment of the plantar fascia to the calcaneus. MRI is a sensitive method for detecting plantar fasciitis, but it is usually not required for establishing the diagnosis.

T e differential diagnosis of inferior heel pain includes calcaneal stress fractures, the spondyloarthritides, rheumatoid arthritis, gout, neoplastic or infiltrative bone processes, and nerve compression/entrapment syndromes.

Resolution of symptoms occurs within 12 months in more than 80% of patients with plantar fasciitis. T e patient is advised to reduce or discontinue activities that can exacerbate plantar fasciitis. Initial treatment consists of ice, heat, massage, and stretching. Orthotics provide medial arch support and can be effective. Foot strapping or taping are commonly performed, and some patients may benefit by wearing a night splint designed to keep the ankle in a neutral position. A short course of NSAIDs can be given to patients when the benefits outweigh the risks. Local glucocorticoid injections have also been shown to be ef cacious but may carry an increased risk for plantar fascia rupture. Plantar fasciotomy is reserved for those patients who have failed to improve after at least 6–12 months of conservative treatment.

Acknowledgment

T is chapter represents a revised version of the chapter authored by Dr. Bruce C. Gilliland that was in the previous editions of Harrison's. Dr. Gilliland passed away on February 17, 2007, and had been a contributor to Harrison's Principles of Internal Medicine since the 11th edition.

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APPENDIX

LABORATORY VALUES OF CLINICAL IMPORTANCE

Alexander Kratz ■ Michael A. Pesce ■ Robert C. Basner ■ Andrew J. Einstein

T is appendix contains tables of reference values for common laboratory tests. A variety of factors can influence reference values. Such variables include the population studied, the duration and means of specimen transport, laboratory methods and instrumentation, and even the type of container used for the collection of the specimen. T e reference or "normal" ranges given in this appendix may therefore not be appropriate for all laboratories, and these values should only be used as general guidelines. Whenever possible, reference values provided by the laboratory performing the testing should be used in the interpretation of laboratory data. Values supplied in this appendix reflect typical reference ranges in nonpregnant adults. Pediatric reference ranges and values in pregnant patients may vary signif cantly from the data presented in the appendix.

In preparing the appendix, the authors have taken into account the fact that the system of international units (SI, système international d'unités) is used in most countries and in some medical journals. However, clinical laboratories may continue to report values in "traditional" or conventional units. T erefore, both systems are provided in the appendix. T e dual system is also used in the text except for those instances in which the numbers remain the same and only the terminology is changed (mmol/L for meq/L or IU/L for mIU/mL), when only the SI units are given.

TABLE 1

HEMATOLOGY AND COAGULATION			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Activated clotting time	WB	70–180 s	70–180 s
Activated protein C resistance (factor V Leiden)	P	Not applicable	Ratio >2.1
ADAMTS13 activity	P	≥0.67	≥67%
ADAMTS13 inhibitor activity	P	Not applicable	≤0.4 U
ADAMTS13 antibody	P	Not applicable	≤18 U
Alpha-2 antiplasmin	P	0.87–1.55	87–155%
Antiphospholipid antibody panel			
PTT-LA (lupus anticoagulant screen)	P	Negative	Negative
Platelet neutralization procedure	P	Negative	Negative
Dilute viper venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 arbitrary units	0–15 GPL
IgM		0–15 arbitrary units	0–15 MPL

(continued)

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Beta-2 glycoprotein 1 antibodies	S		
IgG		0–20 arbitrary units	0–20 SGU
IgM		0–20 arbitrary units	0–20 SMU
Antithrombin III	P		
Antigenic		220–390 mg/L	22–39 mg/dL
Functional		0.7–1.30 U/L	70–130%
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 kIU/L	0.3–0.7 IU/mL
Low-molecular-weight heparin		0.5–1.0 kIU/L	0.5–1.0 IU/mL
Danaparoid (Orgaran)		0.5–0.8 kIU/L	0.5–0.8 IU/mL
Autohemolysis test	WB	0.004–0.045	0.4–4.50%
Autohemolysis test with glucose	WB	0.003–0.007	0.3–0.7%
Bleeding time (adult)		<7.1 min	<7.1 min
C4 binding protein	P	305–695 mg/L	30.5–69.5 mg/dL
	S	275–604 mg/L	27.5–60.4 mg/dL
Clot retraction	WB	0.50–1.00/2 h	50–100%/2 h
Cryofibrinogen	P	Negative	Negative
D-dimer	P	220–740 ng/mL FEU	220–740 ng/mL FEU
Differential blood count	WB		
Relative counts			
Neutrophils		0.40–0.70	40–70%
Bands		0.0–0.05	0–5%
Lymphocytes		0.20–0.50	20–50%
Monocytes		0.04–0.08	4–8%
Eosinophils		0.0–0.6	0–6%
Basophils		0.0–0.02	0–2%
Absolute counts			
Neutrophils		1.42–6.34 × 10^9/L	1420–6340/mm^3
Bands		0–0.45 × 10^9/L	0–450/mm^3
Lymphocytes		0.71–4.53 × 10^9/L	710–4530/mm^3
Monocytes		0.14–0.72 × 10^9/L	140–720/mm^3
Eosinophils		0–0.54 × 10^9/L	0–540/mm^3
Basophils		0–0.18 × 10^9/L	0–180/mm^3
Erythrocyte count	WB		
Adult male		4.30–5.60 × 10^{12}/L	4.30–5.60 × 10^6/mm^3
Adult female		4.00–5.20 × 10^{12}/L	4.00–5.20 × 10^6/mm^3
Erythrocyte life span	WB		
Normal survival		120 days	120 days
Chromium labeled, half-life ($t_{1/2}$)		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Female		0–20 mm/h	0–20 mm/h
Male		0–15 mm/h	0–15 mm/h

(continued)

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Euglobulin lysis time	P	7200–14,400 s	120–240 min
Factor II, prothrombin	P	0.50–1.50	50–150%
Factor V	P	0.50–1.50	50–150%
Factor VII	P	0.50–1.50	50–150%
Factor VIII	P	0.50–1.50	50–150%
Factor IX	P	0.50–1.50	50–150%
Factor X	P	0.50–1.50	50–150%
Factor XI	P	0.50–1.50	50–150%
Factor XII	P	0.50–1.50	50–150%
Factor XIII screen	P	Not applicable	Present
Factor inhibitor assay	P	<0.5 Bethesda units	<0.5 Bethesda units
Fibrin(ogen) degradation products	P	0–1 mg/L	0–1 μg/mL
Fibrinogen	P	2.33–4.96 g/L	233–496 mg/dL
Glucose-6-phosphate dehydrogenase (erythrocyte)	WB	<2400 s	<40 min
Ham's test (acid serum)	WB	Negative	Negative
Hematocrit	WB		
Adult male		0.388–0.464	38.8–46.4
Adult female		0.354–0.444	35.4–44.4
Hemoglobin			
Plasma	P	6–50 mg/L	0.6–5.0 mg/dL
Whole blood	WB		
Adult male		133–162 g/L	13.3–16.2 g/dL
Adult female		120–158 g/L	12.0–15.8 g/dL
Hemoglobin electrophoresis	WB		
Hemoglobin A		0.95–0.98	95–98%
Hemoglobin A_2		0.015–0.031	1.5–3.1%
Hemoglobin F		0–0.02	0–2.0%
Hemoglobins other than A, A_2, or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Immature platelet fraction (IPF)	WB	0.011–0.061	1.1–6.1%
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Leukocytes			
Alkaline phosphatase (LAP)	WB	0.2–1.6 μkat/L	13–100 μ/L
Count (WBC)	WB	$3.54–9.06 \times 10^9$/L	$3.54–9.06 \times 10^3$/mm^3
Mean corpuscular hemoglobin (MCH)	WB	26.7–31.9 pg/cell	26.7–31.9 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	323–359 g/L	32.3–35.9 g/dL
Mean corpuscular hemoglobin of reticulocytes (CH)	WB	24–36 pg	24–36 pg
Mean corpuscular volume (MCV)	WB	79–93.3 fL	79–93.3 μm^3
Mean platelet volume (MPV)	WB	9.00–12.95 fL	9.00–12.95

(continued)

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Osmotic fragility of erythrocytes	WB		
Direct		0.0035–0.0045	0.35–0.45%
Indirect		0.0030–0.0065	0.30–0.65%
Partial thromboplastin time, activated	P	26.3–39.4 s	26.3–39.4 s
Plasminogen	P		
Antigen		84–140 mg/L	8.4–14.0 mg/dL
Functional		0.70–1.30	70–130%
Plasminogen activator inhibitor 1	P	4–43 µg/L	4–43 ng/mL
Platelet aggregation	PRP	Not applicable	>65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid
Platelet count	WB	165–415 × 10^9/L	165–415 × 10^3/mm^3
Platelet, mean volume	WB	6.4–11 fL	6.4–11.0 μm^3
Prekallikrein assay	P	0.50–1.5	50–150%
Prekallikrein screen	P		No deficiency detected
Protein C	P		
Total antigen		0.70–1.40	70–140%
Functional		0.70–1.30	70–130%
Protein S	P		
Total antigen		0.70–1.40	70–140%
Functional		0.65–1.40	65–140%
Free antigen		0.70–1.40	70–140%
Prothrombin gene mutation G20210A	WB	Not applicable	Not present
Prothrombin time	P	12.7–15.4 s	12.7–15.4 s
Protoporphyrin, free erythrocyte	WB	0.28–0.64 µmol/L of red blood cells	16–36 µg/dL of red blood cells
Red cell distribution width	WB	<0.145	<14.5%
Reptilase time	P	16–23.6 s	16–23.6 s
Reticulocyte count	WB		
Adult male		0.008–0.023 red cells	0.8–2.3% red cells
Adult female		0.008–0.020 red cells	0.8–2.0% red cells
Reticulocyte hemoglobin content	WB	>26 pg/cell	>26 pg/cell
Ristocetin cofactor (functional von Willebrand factor)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
Serotonin release assay	S	<0.2 release	<20% release
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	<0.1	<10% hemolysis
Thrombin time	P	15.3–18.5 s	15.3–18.5 s
Thrombin-antithrombin (TAT) complex	P	<4 µg/L	<4 ng/mL

(continued)

TABLE 1

HEMATOLOGY AND COAGULATION (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Total eosinophils	WB	150–300 × 10^6/L	150–300/mm^3
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity			
Plasma	P	1.7–2.1	1.7–2.1
Serum	S	1.4–1.8	1.4–1.8
von Willebrand factor (VWF) antigen (factor VIII:R antigen)	P		
Blood group O		0.75 mean of normal	75% mean of normal
Blood group A		1.05 mean of normal	105% mean of normal
Blood group B		1.15 mean of normal	115% mean of normal
Blood group AB		1.25 mean of normal	125% mean of normal
von Willebrand factor collagen binding	P	590–2490 U/L	59–249 U/dL
von Willebrand factor multimers	P	Normal distribution	Normal distribution
White blood cells: see "Leukocytes"			

Abbreviations: JF, joint fuid; P, plasma; PRP, platelet-rich plasma; S, serum; WB, whole blood.

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Acetoacetate	P	49–294 µmol/L	0.5–3.0 mg/dL
Adrenocorticotropin (ACTH)	P	1.3–16.7 pmol/L	6.0–76.0 pg/mL
Alanine aminotransferase (ALT, SGPT)	S	0.12–0.70 µkat/L	7–41 U/L
Albumin	S	40–50 g/L	4.0–5.0 mg/dL
Aldolase	S	26–138 nkat/L	1.5–8.1 U/L
Aldosterone (adult)			
Supine, normal sodium diet	S, P	<443 pmol/L	<16 ng/dL
Upright, normal	S, P	111–858 pmol/L	4–31 ng/dL
Alpha fetoprotein (adult)	S	0–8.5 µg/L	0–8.5 ng/mL
Alpha-1-acid glycoprotein	S	0.50–1.2 g/L	50–120 mg/dL
Alpha-1 antitrypsin	S	1.0–2.0 g/L	100–200 mg/dL
Ammonia, as NH_3	P	11–35 µmol/L	19–60 µg/dL
Amylase (method dependent)	S	0.34–1.6 µkat/L	20–96 U/L
Androstenedione (adult)	S		
Male		0.81–3.1 nmol/L	23–89 ng/dL
Female			
Premenopausal		0.91–7.5 nmol/L	26–214 ng/dL
Postmenopausal		0.46–2.9 nmol/L	13–82 ng/dL
Angiotensin-converting enzyme (ACE)	S	0.15–1.1 µkat/L	9–67 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S		
Male		0.94–1.78 g/L	94–178 mg/dL
Female		1.01–1.99 g/L	101–199 mg/dL

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Apolipoprotein B	S		
Male		0.55–1.40 g/L	55–140 mg/dL
Female		0.55–1.25 g/L	55–125 mg/dL
Arterial blood gases	WB		
(HCO_3^-)		22–30 mmol/L	22–30 meq/L
Pco_2 (sea level, Fio_2 0.21)		4.7–6.0 kPa	35–45 mmHg
pH		7.35–7.45	7.35–7.45
Po_2 (sea level, Fio_2 0.21, age related)		8.9–13.8 kPa	67–104 mmHg
Carboxyhemoglobin and methemoglobin at pH 7.40 and 37°C		≤0.01	≤1%
Aspartate aminotransferase (AST, SGOT)	S	0.20–0.65 μkat/L	12–38 U/L
Autoantibodies	S		
Anticentromere antibody IgG		≤29 AU/mL	≤29 AU/mL
Antidouble-strand (native) DNA		<25 IU/L	<25 IU/L
Antiglomerular basement membrane antibodies			
Qualitative IgG, IgA		Negative	Negative
Quantitative IgG antibody		≤19 AU/mL	≤19 AU/mL
Antihistone antibodies		<1.0 U	<1.0 U
Anti-Jo-1 antibody		≤29 AU/mL	≤29 AU/mL
Antimitochondrial antibody		Not applicable	<20 units
Antieutrophil cytoplasmic autoantibodies		Not applicable	<1:20
Serine proteinase 3 antibodies		≤19 AU/mL	≤19 AU/mL
Myeloperoxidase antibodies		≤19 AU/mL	≤19 AU/mL
Antinuclear antibody		Not applicable	Negative at 1:40
Antiparietal cell antibody		Not applicable	None detected
Anti-RNP antibody		Not applicable	<1.0 U
Anti-Scl 70 antibody		Not applicable	<1.0 U
Anti-Smith antibody		Not applicable	<1.0 U
Antismooth muscle antibody		Not applicable	<1.0 U
Anti-SSA antibody		Not applicable	<1.0 U
Anti-SSB antibody		Not applicable	Negative
Antithyroglobulin antibody		<40 kIU/mL	<40 IU/mL
Antithyroid peroxidase antibody		<35 kIU/L	<35 IU/L
B-type natriuretic peptide (BNP)	P	Age and gender specific: <100 ng/L	Age and gender specific: <100 pg/mL
Bence Jones protein, serum qualitative	S	Not applicable	None detected
Bence Jones protein, serum quantitative	S		
Free kappa		3.3–19.4 mg/L	0.33–1.94 mg/dL
Free lambda		5.7–26.3 mg/L	0.57–2.63 mg/dL
K/L ratio		0.26–1.65	0.26–1.65
Beta-2-microglobulin	S	1.1–2.4 mg/L	1.1–2.4 mg/L

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Bile acids	S		
Cholic acid		0–1.9 µmol/L	0–1.9 µmol/L
Chenodeoxycholic acid		0–3.4 µmol/L	0–3.4 µmol/L
Deoxycholic acid		0–2.5 µmol/L	0–2.5 µmol/L
Ursodeoxycholic acid		0–1.0 µmol/L	0–1.0 µmol/L
Total		0–7.0 µmol/L	0–7.0 µmol/L
Bilirubin	S		
Total		5.1–22 µmol/L	0.3–1.3 mg/dL
Direct		1.7–6.8 µmol/L	0.1–0.4 mg/dL
Indirect		3.4–15.2 µmol/L	0.2–0.9 mg/dL
C peptide	S	0.27–1.19 nmol/L	0.8–3.5 ng/mL
C1-esterase-inhibitor protein	S	210–390 mg/L	21–39 mg/dL
CA 125	S	<35 kU/L	<35 U/mL
CA 19-9	S	<37 kU/L	<37 U/mL
CA 15-3	S	<33 kU/L	<33 U/mL
CA 27-29	S	0–40 kU/L	0–40 U/mL
Calcitonin	S		
Male		0–7.5 ng/L	0–7.5 pg/mL
Female		0–5.1 ng/L	0–5.1 pg/mL
Calcium	S	2.2–2.6 mmol/L	8.7–10.2 mg/dL
Calcium, ionized	WB	1.12–1.32 mmol/L	4.5–5.3 mg/dL
Carbon dioxide content (TCO_2)	P (sea level)	22–30 mmol/L	22–30 meq/L
Carboxyhemoglobin (carbon monoxide content)	WB		
Nonsmokers (in a nonsmoking environment)		0.0–0.025	0–2.5% of total hemoglobin (Hgb) value
Smokers		0.04–0.09	4–9% of total Hgb value
Loss of consciousness and death		>0.50	>50% of total Hgb value
Carcinoembryonic antigen (CEA)	S		
Nonsmokers		0.0–3.0 µg/L	0.0–3.0 ng/mL
Smokers		0.0–5.0 µg/L	0.0–5.0 ng/mL
Ceruloplasmin	S	250–630 mg/L	25–63 mg/dL
Chloride	S	102–109 mmol/L	102–109 meq/L
Cholesterol (LCL, Total, HDL): Ranges depend on individual patient factors; see 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol			
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chromogranin A	S	0–95 µg/L	0–95 ng/mL
Complement	S		
C3		0.83–1.77 g/L	83–177 mg/dL
C4		0.16–0.47 g/L	16–47 mg/dL
Complement total		60–144 CAE units	60–144 CAE units
Cortisol			
Fasting, 8 am–12 noon	S	138–690 nmol/L	5–25 µg/dL
12 noon–8 pm		138–414 nmol/L	5–15 µg/dL
8 pm–8 am		0–276 nmol/L	0–10 µg/dL
C-reactive protein	S	<10 mg/L	<10 mg/L

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
C-reactive protein, high sensitivity	S	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L	Cardiac risk Low: <1.0 mg/L Average: 1.0–3.0 mg/L High: >3.0 mg/L
Creatine kinase (total)	S		
Females		0.66–4.0 µkat/L	39–238 U/L
Males		0.87−5.0 µkat/L	51–294 U/L
Creatine kinase-MB	S		
Mass		0.0–5.5 µg/L	0.0–5.5 ng/mL
Fraction of total activity (by electrophoresis)		0–0.04	0–4.0%
Creatinine	S		
Female		44–80 µmol/L	0.5–0.9 mg/dL
Male		53–106 µmol/L	0.6–1.2 mg/dL
Cryoglobulins	S	Not applicable	None detected
Cyclic citrullinated peptide (CCP) antibody (IgG)	S	Negative: <20 units Weak positive: 20–39 units Moderate positive: 40–59 Units Strong positive: ≥60 units	Negative: <20 units Weak positive: 20–39 units Moderate positive: 40–59 units Strong positive: ≥60 Units
Cystatin C	S	0.5–1.0 mg/L	0.5–1.0 mg/L
Deamidated gliadin peptide (DGP) antibody, IgA	S		
Negative Weak positive Positive		≤19 units 20–30 units ≥31 units	≤19 units 20–30 units ≥31 units
Deamidated gliadin peptide (DGP) antibody, IgG	S		
Negative Weak positive Positive		≤19 units 20–30 units ≥31 units	≤19 units 20–30 units ≥31 units
Dehydroepiandrosterone (DHEA) (adult)			
Male	S	6.2–43.4 nmol/L	180–1250 ng/dL
Female		4.5–34.0 nmol/L	130–980 ng/dL
Dehydroepiandrosterone (DHEA) sulfate	S		
Male (adult)		100–6190 µg/L	10–619 µg/dL
Female (adult, premenopausal)		120–5350 µg/L	12–535 µg/dL
Female (adult, postmenopausal)		300–2600 µg/L	30–260 µg/dL
11-Deoxycortisol (adult) (compound S)	S	0.34–4.56 nmol/L	12–158 ng/dL
Dihydrotestosterone			
Male	S, P	1.03–2.92 nmol/L	30–85 ng/dL
Female		0.14–0.76 nmol/L	4–22 ng/dL
Dopamine	P	0–130 pmol/L	0–20 pg/mL
Endomysial antibody, IgA	S	<1:10	<1:10
Endomysial antibody, IgG	S	<1:10	<1:10

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)			
ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Epinephrine	P		
Supine (30 min)		<273 pmol/L	<50 pg/mL
Sitting		<328 pmol/L	<60 pg/mL
Standing (30 min)		<491pmol/L	<90 pg/mL
Erythropoietin	S	4–27 U/L	4–27 U/L
Estradiol	S, P		
Female			
Menstruating:			
Follicular phase		74–532 pmol/L	<20–145 pg/mL
Midcycle peak		411–1626 pmol/L	112–443 pg/mL
Luteal phase		74–885 pmol/L	<20–241 pg/mL
Postmenopausal		217 pmol/L	<59 pg/mL
Male		74 pmol/L	<20 pg/mL
Estrone	S, P		
Female			
Menstruating:			
Follicular phase		<555 pmol/L	<150 pg/mL
Luteal phase		<740 pmol/L	<200 pg/mL
Postmenopausal		11–118 pmol/L	3–32 pg/mL
Male		33–133 pmol/L	9–36 pg/mL
Fatty acids, free (nonesterified)	P	0.1–0.6 mmol/L	2.8–16.8 mg/dL
Ferritin	S		
Female		10–150 µg/L	10–150 ng/mL
Male		29−248 µg/L	29–248 ng/mL
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 IU/L	3.0–20.0 mIU/mL
Ovulatory phase		9.0–26.0 IU/L	9.0–26.0 mIU/mL
Luteal phase		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Postmenopausal		18.0–153.0 IU/L	18.0–153.0 mIU/mL
Male		1.0–12.0 IU/L	1.0–12.0 mIU/mL
Fructosamine	S	<285 µmol/L	<285 µmol/L
Galectin-3	S		
Low risk		≤17.8 µg/L	≤17.8 ng/mL
Intermediate risk		17.9–25.9 µg/L	17.9–25.9 ng/mL
Higher risk		>25.9 µg/L	>25.9 ng/mL
Gamma glutamyltransferase	S	0.15–0.99 µkat/L	9–58 U/L
Gastrin	S	<100 ng/L	<100 pg/mL
Glucagon	P	40–130 ng/L	40–130 pg/mL
Glucose	WB	3.6–5.3 mmol/L	65–95 mg/dL
Glucose (fasting)	P		
Normal		4.2–5.6 mmol/L	75–100 mg/dL
Increased risk for diabetes		5.6–6.9 mmol/L	100–125 mg/dL

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Diabetes mellitus		Fasting ≥7.0 mmol/L	Fasting ≥126 mg/dL
		A 2-h level of ≥11.1 mmol/L during an oral glucose tolerance test	A 2-h level of ≥200 mg/dL during an oral glucose tolerance test
		A random glucose level of ≥11.1 mmol/L in patients with symptoms of hyperglycemia	A random glucose level of ≥200 mg/dL in patients with symptoms of hyperglycemia
Growth hormone	S	0–5 µg/L	0–5 ng/mL
Hemoglobin A_{1c}	WB	0.04–0.06 Hgb fraction	4.0–5.6%
Prediabetes		0.057–0.064 Hgb fraction	5.7–6.4%
Diabetes mellitus		A hemoglobin A_{1c} level of ≥0.065 Hgb fraction as suggested by the American Diabetes Association	A hemoglobin A_{1c} level of ≥6.5% as suggested by the American Diabetes Association
Hemoglobin A_{1c} with estimated average glucose (eAG)	WB	eAg (mmoL/L) = 1.59 × HbA_{1c} – 2.59	eAg (mg/dL) = 28.7 × HbA_{1c} – 46.7
Homocysteine	P	4.4–10.8 µmol/L	4.4–10.8 µmol/L
Human chorionic gonadotropin (HCG)	S		
Nonpregnant female		<5 IU/L	<5 mIU/mL
1–2 weeks postconception		9–130 IU/L	9–130 mIU/mL
2–3 weeks postconception		75–2600 IU/L	75–2600 mIU/mL
3–4 weeks postconception		850–20,800 IU/L	850–20,800 mIU/mL
4–5 weeks postconception		4000–100,200 IU/L	4000–100,200 mIU/mL
5–10 weeks postconception		11,500–289,000 IU/L	11,500–289,000 mIU/mL
10–14 weeks postconception		18,300–137,000 IU/L	18,300–137,000 mIU/mL
Second trimester		1400–53,000 IU/L	1400–53,000 mIU/mL
Third trimester		940–60,000 IU/L	940–60,000 mIU/mL
Human epididymis protein 4 (HE-4)	S	0–150 pmol/L	0–150 pmol/L
β-Hydroxybutyrate	P	60–170 µmol/L	0.6–1.8 mg/dL
17-Hydroxyprogesterone (adult)	S		
Male		<4.17 nmol/L	<139 ng/dL
Female			
Follicular phase		0.45–2.1 nmol/L	15–70 ng/dL
Luteal phase		1.05–8.7 nmol/L	35–290 ng/dL
Immunofixation	S	Not applicable	No bands detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.70–3.50 g/L	70–350 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	1–87 kIU/L	1–87 IU/mL
IgG	S	7.0–17.0 g/L	700–1700 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.50–3.0 g/L	50–300 mg/dL

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Inhibin A	S		
Males		≤2.0 ng/L	≤2.0 pg/mL
Females			
Early follicular phase		1.8–17.3 ng/L	1.8–17.3 pg/mL
Mid follicular phase		3.5–31.7 ng/L	3.5–17.3 pg/mL
Late follicular phase		9.8–90.3 ng/L	9.8–90.3 pg/mL
Midcycle		16.9–91.8 ng/L	16.9–91.8 pg/mL
Early luteal phase		16.1–97.5 ng/L	16.1–97.5 pg/mL
Mid luteal phase		3.9–87.7 ng/L	3.9–87.7 pg/mL
Late luteal phase		2.7–47.1 ng/L	2.7–47.1 pg/mL
Postmenopausal		<1.0–2.1 ng/L	<1.0–2.1 pg/mL
Insulin	S, P	14.35–143.5 pmol/L	2–20 µU/mL
Iron	S	7–25 µmol/L	41–141 µg/dL
Iron-binding capacity	S	45–73 µmol/L	251–406 µg/dL
Iron-binding capacity saturation	S	0.16–0.35	16–35%
Ischemia-modified albumin	S	<85 kU/L	<85 U/mL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
Ketone (acetone)	S	Negative	Negative
Lactate	P, arterial	0.5–1.6 mmol/L	4.5–14.4 mg/dL
	P, venous	0.5–2.2 mmol/L	4.5–19.8 mg/dL
Lactate dehydrogenase	S	2.0–3.8 µkat/L	115–221 U/L
Lamellar body count	AMF		
Immature		<15,000/µL	<15,000/µL
Indeterminate		15,000–50,000/µL	15,000-50,000/µL
Mature		>50,000/µL	>50,000/µL
Lecithin/sphingomyelin (L/S) ratio	AMF		
Immature		≤1.5	≤1.5
Transitional		1.5–1.9	1.5–1.9
Mature		≥2.0–2.5	≥2.0–2.5
Lipase	S	0.51–0.73 µkat/L	3–43 U/L
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Lipoprotein-associated phospholipase A2	S, P	0–234 µg/L	0–234 ng/mL
Luteinizing hormone (LH)	S, P		
Female			
Menstruating			
Follicular phase		2.0–15.0 U/L	2.0–15.0 mIU/mL
Ovulatory phase		22.0–105.0 U/L	22.0–105.0 mIU/mL
Luteal phase		0.6–19.0 U/L	0.6–19.0 mIU/mL
Postmenopausal		16.0–64.0 U/L	16.0–64.0 mIU/mL
Male		2.0–12.0 U/L	2.0–12.0 mIU/mL
Magnesium	S	0.62–0.95 mmol/L	1.5–2.3 mg/dL
Metanephrine	P	<0.5 nmol/L	<100 pg/mL
Methemoglobin	WB	0.0–0.01	0–1% of total Hgb value
Myoglobin	S		
Male		20–71 µg/L	20–71 µg/L
Female		25–58 µg/L	25–58 µg/L

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Norepinephrine	P		
Supine (30 min)		650–2423 pmol/L	110–410 pg/mL
Sitting		709–4019 pmol/L	120–680 pg/mL
Standing (30 min)		739–4137 pmol/L	125–700 pg/mL
N-telopeptide (cross-linked), NTx	S		
Female, premenopausal		6.2–19.0 nmol BCE	6.2–19.0 nmol BCE
Male		5.4–24.2 nmol BCE	5.4–24.2 nmol BCE
NT-proBNP	S, P	<125 ng/Lup to 75 years	<125 pg/mLup to 75 years
		<450 ng/L>75 years	<450 pg/mL>75 years
5' Nucleotidase	S	0.00–0.19 µkat/L	0–11 U/L
Osmolality	P	275–295 mOsmol/kg serum water	275–295 mOsmol/kg serum water
Osteocalcin	S	11–50 µg/L	11–50 ng/mL
Oxygen content (age and gender related)	WB		
Arterial (sea level)		17–21 mL/dL	17–21 vol%
Venous (sea level)		10–16 mL/dL	10–16 vol%
Oxygen saturation (sea level)	WB	Fraction:	Percent:
Arterial		0.91–1.0	91–100%
Venous, arm		0.60–0.85	60–85%
Parathyroid hormone (intact)	S	8–51 ng/L	8–51 pg/mL
Phosphatase, alkaline	S	0.56–1.63 µkat/L	33–96 U/L
Phosphatase, alkaline bone	S		
Male		≤20 µg/L	≤20 ng/mL
Female			
Premenopausal Postmenopausal		≤14 µg/L ≤22 µg/L	≤14 ng/mL ≤22 ng/mL
Phosphorus, inorganic	S	0.81–1.4 mmol/L	2.5–4.3 mg/dL
Potassium	S	3.5–5.0 mmol/L	3.5–5.0 meq/L
Prealbumin (transthyretin)	S	170–340 mg/L	17–34 mg/dL
Procalcitonin	S	<0.1 µg/L	<0.1 ng/mL
Progesterone	S, P		
Female: (follicular)		<3.18 nmol/L	<1.0 ng/mL
Midluteal		9.54–63.6 nmol/L	3–20 ng/mL
Male		<3.18 nmol/L	<1.0 ng/mL
Prolactin	S		
Male		53–360 mg/L	2.5–17 ng/mL
Female		40–530 mg/L	1.9–25 ng/mL
Prostate-specific antigen (PSA)	S	0.0–4.0 µg/L	0.0–4.0 ng/mL
Prostate-specific antigen, free	S	With total PSA between 4 and 10 µg/Land when the free PSA is:	With total PSA between 4 and 10 ng/mLand when the free PSA is:

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
		>0.25 decreased risk of prostate cancer	>25% decreased risk of prostate cancer
		<0.10 increased risk of prostate cancer	<10% increased risk of prostate cancer
Protein fractions:	S		
Albumin		35–55 g/L	3.5–5.5 g/dL (50–60%)
Globulin		20–35 g/L	2.0–3.5 g/dL (40–50%)
Alpha-1		2–4 g/L	0.2–0.4 g/dL (4.2–7.2%)
Alpha-2		5–9 g/L	0.5–0.9 g/dL (6.8–12%)
Beta		6–11 g/L	0.6–1.1 g/dL (9.3–15%)
Gamma		7–17 g/L	0.7–1.7 g/dL (13–23%)
Protein, total	S	67–86 g/L	6.7–8.6 g/dL
Pyruvate	P	40–130 µmol/L	0.35–1.14 mg/dL
Retinol-binding protein	S	0.71–2.9 µmol/L	1.5–6.0 mg/dL
Rheumatoid factor	S	<15 kIU/L	<15 IU/mL
Serotonin	WB	0.28–1.14 µmol/L	50–200 ng/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern
Sex hormone–binding globulin (adult)	S		
Male		11–80 nmol/L	11–80 nmol/L
Female		30–135 nmol/L	30–135 nmol/L
Sodium	S	136–146 mmol/L	136–146 meq/L
Somatomedin-C (IGF-1) (adult)	S		
16 years		226–903 µg/L	226–903 ng/mL
17 years		193–731 µg/L	193–731 ng/mL
18 years		163–584 µg/L	163–584 ng/mL
19 years		141–483 µg/L	141–483 ng/mL
20 years		127–424 µg/L	127–424 ng/mL
21–25 years		116–358 µg/L	116–358 ng/mL
26–30 years		117–329 µg/L	117–329 ng/mL
31–35 years		115–307 µg/L	115–307 ng/mL
36–40 years		119–204 µg/L	119–204 ng/mL
41–45 years		101–267 µg/L	101–267 ng/mL
46–50 years		94–252 µg/L	94–252 ng/mL
51–55 years		87–238 µg/L	87–238 ng/mL
56–60 years		81–225 µg/L	81–225 ng/mL
61–65 years		75–212 µg/L	75–212 ng/mL
66–70 years		69–200 µg/L	69–200 ng/mL
71–75 years		64–188 µg/L	64–188 ng/mL
76–80 years		59–177 µg/L	59–177 ng/mL
81–85 years		55–166 µg/L	55–166 ng/mL
Somatostatin	P	<25 ng/L	<25 pg/mL
Testosterone, free			

(continued)

TABLE 2

CLINICAL CHEMISTRY AND IMMUNOLOGY (CONTINUED)

ANALYTE	SPECIMEN	SI UNITS	CONVENTIONAL UNITS
Female, adult	S	10.4–65.9 pmol/L	3–19 pg/mL
Male, adult		312–1041 pmol/L	90–300 pg/mL
Testosterone, total,	S		
Female		0.21–2.98 nmol/L	6–86 ng/dL
Male		9.36–37.10 nmol/L	270–1070 ng/dL
Thyroglobulin	S	13–318 µg/L	1.3–31.8 ng/mL
Thyroid-binding globulin	S	13–30 mg/L	1.3–3.0 mg/dL
Thyroid-stimulating hormone (thyrotropin)	S	0.34–4.25 mIU/L	0.34–4.25 µIU/mL
Thyrotropin receptor antibody	S	≤1.75 IU/L	≤1.75 mIU/mL
Thyroxine, free (fT_4)	S	9.0–16 pmol/L	0.7–1.24 ng/dL
Thyroxine, total (T_4)	S	70–151 nmol/L	5.4–11.7 µg/dL
Thyroxine index (free)	S	6.7–10.9	6.7–10.9
Tissue transglutaminase (tTG) antibody, IgA	S		
Negative Weak positive Positive		<4.0 U/mL 4.0–10.0 U/mL >10.0 U/mL	<4.0 U/mL 4.0–10.0 U/mL >10.0 U/mL
Tissue transglutaminase (tTG) antibody, IgG	S		
Negative Weak positive Positive		<6.0 U/mL 6.0–9.0 U/mL >9.0 U/mL	<6.0 U/mL 6.0–9.0 U/mL >9.0 U/mL
Transferrin	S	2.0–4.0 g/L	200–400 mg/dL
Transferrin, carbohydrate deficient, for alcohol use	S	0.017	1.7%
Triglycerides	S	0.34–2.26 mmol/L	30–200 mg/dL
Triiodothyronine, free (fT_3)	S	3.7–6.5 pmol/L	2.4–4.2 pg/mL
Triiodothyronine, total (T_3)	S	1.2–2.1 nmol/L	77–135 ng/dL
Troponin I	S, P		
99th percentile of a healthy population		Method-dependent	Method-dependent
Troponin T	S, P		
99th percentile of a healthy population		0–14 ng/L	0–14 ng/L
Urea nitrogen	S	2.5–7.1 mmol/L	7–20 mg/dL
Uric acid	S		
Female		0.15–0.33 mmol/L	2.5–5.6 mg/dL
Male		0.18–0.41 mmol/L	3.1–7.0 mg/dL
Vasoactive intestinal polypeptide	P	0–60 ng/L	0–60 pg/mL
Zinc protoporphyrin (ZPP)	WB	0–400 µg/L	0–40 µg/dL
ZPP-to-heme ratio	WB	0–69 µmol ZPP/mol heme	0–69 µmol ZPP/mol heme

Abbreviations: AMF, amniotic fuid; BCE, bone collagen equivalent; P, plasma; S, serum; WB, whole blood.
Source: NJ Stone et al: J Am Coll Cardiol 63:2889–2934, 2014.

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Acetaminophen	66–199 µmol/L	10–30 µg/mL	>1320 µmol/L	>200 µg/mL
Amikacin				
Peak	34–51 µmol/L	20–30 µg/mL	>60 µmol/L	>35 µg/mL
Trough	0–17 µmol/L	0–10 µg/mL	>17 µmol/L	>10 µg/mL
Amitriptyline/nortriptyline (total drug)	430–900 nmol/L	120–250 ng/mL	>1800 nmol/L	>500 ng/mL
Amphetamine	150–220 nmol/L	20–30 ng/mL	>1500 nmol/L	>200 ng/mL
Bromide	9.4–18.7 mmol/L	75–150 mg/dL	>18.8 mmol/L	>150 mg/dL
Mild toxicity			6.4–18.8 mmol/L	51–150 mg/dL
Severe toxicity			>18.8 mmol/L	>150 mg/dL
Lethal			>37.5 mmol/L	>300 mg/dL
Caffeine	25.8–103 µmol/L	5–20 µg/ml	>206 µmol/L	>40 µg/mL
Carbamazepine	17–42 µmol/L	4–10 µg/mL	> 85 µmol/L	>20 µg/mL
Chloramphenicol				
Peak	31–62 µmol/L	10–20 µg/mL	>77 µmol/L	>25 µg/mL
Trough	15–31 µmol/L	5–10 µg/mL	>46 µmol/L	>15 µg/mL
Chlordiazepoxide	1.7–10 µmol/L	0.5–3.0 µg/mL	>17 µmol/L	>5.0 µg/mL
Clonazepam	32–240 nmol/L	10–75 ng/mL	>320 nmol/L	>100 ng/mL
Clozapine	0.6–2.1 µmol/L	200–700 ng/mL	>3.7 µmol/L	>1200 ng/mL
Cocaine			>3.3 µmol/L	>1.0 µg/mL
Codeine	43–110 nmol/mL	13–33 ng/mL	>3700 nmol/mL	>1100 ng/mL(lethal)
Cyclosporine				
Renal transplant				
0–6 months	208–312 nmol/L	250–375 ng/mL	>312 nmol/L	>375 ng/mL
6–12 months after transplant	166–250 nmol/L	200–300 ng/mL	>250 nmol/L	>300 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	>150 ng/mL
Cardiac transplant				
0–6 months	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
6–12 months after transplant	125–208 nmol/L	150–250 ng/mL	>208 nmol/L	>250 ng/mL
>12 months	83–125 nmol/L	100–150 ng/mL	>125 nmol/L	150 ng/mL
Lung transplant				
0–6 months	250–374 nmol/L	300–450 ng/mL	>374 nmol/L	>450 ng/mL
Liver transplant				
Initiation	208–291 nmol/L	250–350 ng/mL	>291 nmol/L	>350 ng/mL
Maintenance	83–166 nmol/L	100–200 ng/mL	>166 nmol/L	>200 ng/mL
Desipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Diazepam (and metabolite)				
Diazepam	0.7 –3.5 µmol/L	0.2–1.0 µg/mL	>7.0 µmol/L	>2.0 µg/mL
Nordiazepam	0.4– 6.6 µmol/L	0.1–1.8 µg/mL	>9.2 µmol/L	>2.5 µg/mL
Digoxin	0.64–1.6 nmol/L	0.5–1.2 ng/mL	>3.1 nmol/L	>2.4 ng/mL

(continued)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Disopyramide	5.3–14.7 µmol/L	2–5 µg/mL	>20.6 µmol/L	>7 µg/mL
Doxepin and nordoxepin				
Doxepin	0.36–0.98 µmol/L	101–274 ng/mL	>1.8 µmol/L	>503 ng/mL
Nordoxepin	0.38–1.04 µmol/L	106–291 ng/mL	>1.9 µmol/L	>531 ng/mL
Ethanol				
Behavioral changes			>4.3 mmol/L	>20 mg/dL
Legal limit			≥17 mmol/L	≥80 mg/dL
Critical with acute exposure			>54 mmol/L	>250 mg/dL
Ethylene glycol				
Toxic			>2 mmol/L	>12 mg/dL
Lethal			>20 mmol/L	>120 mg/dL
Ethosuximide	280–700 µmol/L	40–100 µg/mL	>700 µmol/L	>100 µg/mL
Everolimus (trough)				
Kidney transplant	3.1–8.34 nmol/L	3–8 ng/mL	>12.5 nmol/L	>12 ng/mL
Oncology	5.2–10.4 nmol/L	5.0–10.0 ng/mL	>12.5 nmol/L	>12 ng/mL
Felbamate (trough)	126–252 µmol/L	30–60 µg/mL	Toxic range not well established	
Flecainide	0.5–2.4 µmol/L	0.2–1.0 µg/mL	>3.6 µmol/L	>1.5 µg/mL
Gabapentin (trough)	11.7–116.8 µmol/L	2–20 µg/mL	Toxic range not well established	
Gentamicin				
Peak	10–21 µmol/mL	5–10 µg/mL	>25 µmol/mL	>12 µg/mL
Trough	0–4.2 µmol/mL	0–2 µg/mL	>4.2 µmol/mL	>2 µg/mL
Heroin (diacetyl morphine)			>700 µmol/L	>200 ng/mL (as morphine)
Ibuprofen	49–243 µmol/L	10–50 µg/mL	>970 µmol/L	>200 µg/mL
Imipramine (and metabolites)				
Desimipramine	375–1130 nmol/L	100–300 ng/mL	>1880 nmol/L	>500 ng/mL
Total imipramine + desimipramine	563–1130 nmol/L	150–300 ng/mL	>1880 nmol/L	>500 ng/mL
Isopropanol			>8.3 mmol/L	>50 mg/dL
Lamotrigine	11.7–54.7 µmol/L	3–14 µg/mL	>58.7 µmol/L	>15 µg/mL
Levetiracetam (Keppra)	29–176 µmol/L	5–30 µg/mL	Toxic range not well established	
Lidocaine	5.1–21.3 µmol/L	1.2–5.0 µg/mL	>38.4 µmol/L	>9.0 µg/mL
Lithium	0.5–1.3 mmol/L	0.5–1.3 meq/L	>2 mmol/L	>2 meq/L
Methadone	1.0–3.2 µmol/L	0.3–1.0 µg/mL	>6.5 µmol/L	>2 µg/mL
Methamphetamine	0.07–0.34 µmol/L	0.01–0.05 µg/mL	>3.35 µmol/L	>0.5 µg/mL
Methanol			>6 mmol/L	>20 mg/dL
Methotrexate				
Low-dose	0.01–0.1 µmol/L	0.01–0.1 µmol/L	>0.1 µmol/L	>0.1 µmol/L
High-dose (24 h)	<5.0 µmol/L	<5.0 µmol/L	>5.0 µmol/L	>5.0 µmol/L
High-dose (48 h)	<0.50 µmol/L	<0.50 µmol/L	>0.5 µmol/L	>0.5 µmol/L
High-dose (72 h)	<0.10 µmol/L	<0.10 µmol/L	>0.1 µmol/L	>0.1 µmol/L

(continued)

TABLE 3

TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (CONTINUED)

	THERAPEUTIC RANGE		TOXIC LEVEL	
DRUG	SI UNITS	CONVENTIONAL UNITS	SI UNITS	CONVENTIONAL UNITS
Morphine	232–286 µmol/L	65–80 ng/mL	>720 µmol/L	>200 ng/mL
Mycophenolic acid	3.1–10.9 µmol/L	1.0–3.5 ng/mL	>37 µmol/L	>12 ng/mL
Nitroprusside (as thiocyanate)	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nortriptyline	190–569 nmol/L	50–150 ng/mL	>1900 nmol/L	>500 ng/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>258 µmol/L	>60 µg/mL
Phenytoin	40–79 µmol/L	10–20 µg/mL	>158 µmol/L	>40 µg/mL
Phenytoin, free	4.0–7.9 µg/mL	1–2 µg/mL	>13.9 µg/mL	>3.5 µg/mL
% Free	0.08–0.14	8–14%		
Primidone and metabolite				
Primidone	23–55 µmol/L	5–12 µg/mL	>69 µmol/L	>15 µg/mL
Phenobarbital	65–172 µmol/L	15–40 µg/mL	>215 µmol/L	>50 µg/mL
Procainamide				
Procainamide	17–42 µmol/L	4–10 µg/mL	>43 µmol/L	>10 µg/mL
NAPA (N-acetylprocainamide)	22–72 µmol/L	6–20 µg/mL	>126 µmol/L	>35 µg/mL
Quinidine	6.2–15.4 µmol/L	2.0–5.0 µg/mL	>19 µmol/L	>6 µg/mL
Salicylates	145–2100 µmol/L	2–29 mg/dL	>2900 µmol/L	>40 mg/dL
Sirolimus (trough level)				
Kidney transplant	4.4–15.4 nmol/L	4–14 ng/mL	>16 nmol/L	>15 ng/mL
Tacrolimus (FK506) (trough)				
Kidney and liver transplant				
Initiation	12–19 nmol/L	10–15 ng/mL	>25 nmol/L	>20 ng/mL
Maintenance	6–12 nmol/L	5–10 ng/mL	>25 nmol/L	>20 ng/mL
Heart transplant				
Initiation	19–25 nmol/L	15–20 ng/mL		
Maintenance	6–12 nmol/L	5–10 ng/mL		
Theophylline	56–111 µg/mL	10–20 µg/mL	>168 µg/mL	>30 µg/mL
Thiocyanate				
After nitroprusside infusion	103–499 µmol/L	6–29 µg/mL	860 µmol/L	>50 µg/mL
Nonsmoker	17–69 µmol/L	1–4 µg/mL		
Smoker	52–206 µmol/L	3–12 µg/mL		
Tobramycin				
Peak	11–22 µg/L	5–10 µg/mL	>26 µg/L	>12 µg/mL
Trough	0–4.3 µg/L	0–2 µg/mL	>4.3 µg/L	>2 µg/mL
Topiramate (trough)	5.9–58.9 µmol/L	2.0–20.0 µg/mL	Toxic range not well established	
Valproic acid	346–693 µmol/L	50–100 µg/mL	>693 µmol/L	>100 µg/mL
Vancomycin				
Peak	14–28 µmol/L	20–40 µg/mL	>55 µmol/L	>80 µg/mL
Trough	3.5–10.4 µmol/L	5–15 µg/mL	>14 µmol/L	>20 µg/mL
Zonisamide (trough)	47–188 µmol/L	10–40 µg/mL	Toxic range not well established	

TABLE 4

VITAMINS AND SELECTED TRACE MINERALS

		REFERENCE RANGE	
SPECIMEN	ANALYTE	SI UNITS	CONVENTIONAL UNITS
Aluminum	S	<0.2 µmol/L	<5.41 µg/L
Arsenic	WB	0.0–0.17 µmol/L	0–13 µg/L
Cadmium	WB	<44.5 nmol/L	<5.0 µg/L
Coenzyme Q10 (ubiquinone)	P	433–1532 µg/L	433–1532 µg/L
β-Carotene	S	0.07–1.43 µmol/L	4–77 µg/dL
Copper	S	11–22 µmol/L	70–140 µg/dL
Folic acid	RC	340–1020 nmol/Lcells	150–450 ng/mLcells
Folic acid	S	12.2–40.8 nmol/L	5.4–18.0 ng/mL
Lead	S		
Adult		<0.5 µmol/L	<10 µg/dL
Children		<0.25 µmol/L	<5 µg/dL
Mercury	WB	0–50 µmol/L	0–10 µg/L
Selenium	S	0.8–2.0 µmol/L	63–160 µg/L
Vitamin A	S	0.7–3.5 µmol/L	20–100 µg/dL
Vitamin B_1 (thiamine)	S	0–75 nmol/L	0–2 µg/dL
Vitamin B_2 (riboflavin)	S	106–638 nmol/L	4–24 µg/dL
Vitamin B_6	P	20–121 nmol/L	5–30 ng/mL
Vitamin B_{12}	S	206–735 pmol/L	279–996 pg/mL
Vitamin C (ascorbic acid)	S	23–57 µmol/L	0.4–1.0 mg/dL
Vitamin D 1,25-dihydroxy, total	S, P	36–180 pmol/L	15–75 pg/mL
Vitamin D 25-hydroxy, total	P	75–250 nmol/L	30–100 ng/mL
Vitamin E	S	12–42 µmol/L	5–18 µg/mL
Vitamin K	S	0.29–2.64 nmol/L	0.13–1.19 ng/mL
Zinc	S	11.5–18.4 µmol/L	75–120 µg/dL

Abbreviations: P, plasma; RC, red cells; S, serum; WB, whole blood.

TABLE 5

CEREBROSPINAL FLUID[a]

CONSTITUENT	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Osmolarity	292–297 mmol/kg water	292–297 mOsm/L
Electrolytes		
Sodium	137–145 mmol/L	137–145 meq/L
Potassium	2.7–3.9 mmol/L	2.7–3.9 meq/L
Calcium	1.0–1.5 mmol/L	2.1–3.0 meq/L
Magnesium	1.0–1.2 mmol/L	2.0–2.5 meq/L
Chloride	116–122 mmol/L	116–122 meq/L
CO_2 content	20–24 mmol/L	20–24 meq/L
Pco_2	6–7 kPa	45–49 mmHg
pH	7.31–7.34	
Glucose	2.22–3.89 mmol/L	40–70 mg/dL
Lactate	1–2 mmol/L	10–20 mg/dL
Total protein:		
Lumbar	0.15–0.5 g/L	15–50 mg/dL
Cisternal	0.15–0.25 g/L	15–25 mg/dL
Ventricular	0.06–0.15 g/L	6–15 mg/dL
Albumin	0.066–0.442 g/L	6.6–44.2 mg/dL
IgG	0.009–0.057 g/L	0.9–5.7 mg/dL
IgG index[b]	0.29–0.59	
Oligoclonal bands (OGB)	<2 bands not present in matched serum sample	
Ammonia	15–47 µmol/L	25–80 µg/dL
Creatinine	44–168 µmol/L	0.5–1.9 mg/dL
Myelin basic protein	<4 µg/L	
Cerebrospinal fuid pressure		50–180 mmH_2O
Cerebrospinal fuid volume (adult)	~150 mL	
Red blood cells	0	0
Leukocytes		
Total	0–5 mononuclear cells per µL	
Differential		
Lymphocytes	60–70%	
Monocytes	30–50%	
Neutrophils	None	

[a]Since cerebrospinal fuid (CSF) concentrations are equilibrium values, measurements of the same parameters in blood plasma obtained at the same time are recommended. However, there is a time lag in attainment of equilibrium, and cerebrospinal levels of plasma constituents that can fuctuate rapidly (such as plasma glucose) may not achieve stable values until after a significant lag phase.

[b]IgG index = CSF IgG (mg/dL) × serum albumin (g/dL)/serum IgG (g/dL) × CSF albumin (mg/dL).

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Acidity, titratable	20–40 mmol/d	20–40 meq/d
Aldosterone	Normal diet: 6–25 µg/d	Normal diet: 6–25 µg/d
	Low-salt diet: 17–44 µg/d	Low-salt diet: 17–44 µg/d
	High-salt diet: 0–6 µg/d	High-salt diet: 0–6 µg/d
Aluminum	0.19–1.11 µmol/L	5–30 µg/L
Ammonia	30–50 mmol/d	30–50 meq/d
Amylase		4–400 U/L
Amylase/creatinine clearance ratio ($[Cl_{am}/Cl_{cr}] \times 100$)	1–5	1–5
Arsenic	0.07–0.67 µmol/d	5–50 µg/d
Bence Jones protein, urine, qualitative	Not applicable	None detected
Bence Jones protein, urine, quantitative		
Free kappa	1.4–24.2 mg/L	0.14–2.42 mg/dL
Free lambda	0.2–6.7 mg/L	0.02–0.67 mg/dL
K/L ratio	2.04–10.37	2.04–10.37
Calcium (10 meq/d or 200 mg/d dietary calcium)	<7.5 mmol/d	<300 mg/d
Chloride	140–250 mmol/d	140–250 mmol/d
Citrate	320–1240 mg/d	320–1240 mg/d
Copper	<0.95 µmol/d	<60 µg/d
Coproporphyrins (types I and III)	0–20 µmol/mol creatinine	0–20 µmol/mol creatinine
Cortisol, free	55–193 nmol/d	20–70 µg/d
Creatine, as creatinine		
Female	<760 µmol/d	<100 mg/d
Male	<380 µmol/d	<50 mg/d
Creatinine	8.8–14 mmol/d	1.0–1.6 g/d
Dopamine	392–2876 nmol/d	60–440 µg/d
Eosinophils	<100 eosinophils/mL	<100 eosinophils/mL
Epinephrine	0–109 nmol/d	0–20 µg/d
Glomerular filtration rate	>60 mL/min/1.73 m^2	>60 mL/min/1.73 m^2
	For African Americans, multiply the result by 1.21	For African Americans, multiply the result by 1.21
Glucose (glucose oxidase method)	0.3–1.7 mmol/d	50–300 mg/d
5-Hydroindoleacetic acid (5-HIAA)	0–78.8 µmol/d	0–15 mg/d
Hydroxyproline	53–328 µmol/d	53–328 µmol/d
Iodine, spot urine		
WHO classification of iodine deficiency:		
Not iodine deficient	>100 µg/L	>100 µg/L
Mild iodine deficiency	50–100 µg/L	50–100 µg/L
Moderate iodine deficiency	20–49 µg/L	20–49 µg/L
Severe iodine deficiency	<20 µg/L	<20 µg/L
Ketone (acetone)	Negative	Negative
17 Ketosteroids	3–12 mg/d	3–12 mg/d

(continued)

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Metanephrines		
Metanephrine	30–350 µg/d	30–350 µg/d
Normetanephrine	50–650 µg/d	50–650 µg/d
Microalbumin		
Normal	0.0–0.03 g/d	0–30 mg/d
Microalbuminuria	0.03–0.30 g/d	30–300 mg/d
Clinical albuminuria	>0.3 g/d	>300 mg/d
Microalbumin/creatinine ratio		
Normal	0–3.4 g/mol creatinine	0–30 µg/mg creatinine
Microalbuminuria	3.4–34 g/mol creatinine	30–300 µg/mg creatinine
Clinical albuminuria	>34 g/mol creatinine	>300 µg/mg creatinine
β_2-Microglobulin	0–160 µg/L	0–160 µg/L
Norepinephrine	89–473 nmol/d	15–80 µg/d
N-telopeptide (cross-linked), NTx		
Female, premenopausal	17–94 nmol BCE/mmol creatinine	17–94 nmol BCE/mmol creatinine
Female, postmenopausal	26–124 nmol BCE/mmol creatinine	26–124 nmol BCE/mmol creatinine
Male	21–83 nmol BCE/mmol creatinine	21–83 nmol BCE/mmol creatinine
Osmolality	100–800 mosm/kg	100–800 mosm/kg
Oxalate		
Male	80–500 µmol/d	7–44 mg/d
Female	45–350 µmol/d	4–31 mg/d
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus) (varies with intake)	12.9–42.0 mmol/d	400–1300 mg/d
Porphobilinogen	None	None
Potassium (varies with intake)	25–100 mmol/d	25–100 meq/d
Protein	<0.15 g/d	<150 mg/d
Protein/creatinine ratio	Male: 15–68 mg/g Female: 10–107 mg/g	Male: 15–68 mg/g Female: 10–107 mg/g
Sediment		
Red blood cells	0–2/high-power field	
White blood cells	0–2/high-power field	
Bacteria	None	
Crystals	None	
Bladder cells	None	
Squamous cells	None	
Tubular cells	None	
Broad casts	None	
Epithelial cell casts	None	
Granular casts	None	

(continued)

TABLE 6

URINE ANALYSIS AND RENAL FUNCTION TESTS (CONTINUED)

	REFERENCE RANGE	
	SI UNITS	CONVENTIONAL UNITS
Hyaline casts	0–5/low-power field	
Red blood cell casts	None	
Waxy casts	None	
White cell casts	None	
Sodium (varies with intake)	100–260 mmol/d	100–260 meq/d
Specific gravity:		
After 12-h fuid restriction	>1.025	>1.025
After 12-h deliberate water intake	≤1.003	≤1.003
Tubular reabsorption, phosphorus	0.79–0.94 of filtered load	79–94% of filtered load
Urea nitrogen	214–607 mmol/d	6–17 g/d
Uric acid (normal diet)	1.49–4.76 mmol/d	250–800 mg/d
Vanillylmandelic acid (VMA)	<30 µmol/d	<6 mg/d

Abbreviation: BCE, bone collagen equivalent.

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REVIEW AND SELF-ASSESSMENT*

Charles M. Wiener ■ Cynthia D. Brown ■ Brian Houston

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

1. All of the following are key features of the innate immune system EXCEPT:

A. Exclusively a feature of vertebrate animals
B. Important cells include macrophages and natural killer lymphocytes
C. Nonrecognition of benign foreign molecules or microbes
D. Recognition by germline-encoded host molecules
E. Recognition of key microbe virulence factors but no recognition of self-molecules

2. A 29-year-old man with episodic abdominal pain and stress-induced edema of the lips, tongue, and occasionally larynx is likely to have low functional or absolute levels of which of the following proteins?

A. C1 esterase inhibitor
B. C5A (complement cascade)
C. Cyclooxygenase
D. Immunoglobulin (Ig) E
E. T-cell receptor, α chain

3. Which of the following statements best describes the function of proteins encoded by the human major histocompatibility complex (MHC) I and II genes?

A. Activation of the complement system
B. Binding to cell surface receptors on granulocytes and macrophages to initiate phagocytosis
C. Nonspecific binding of antigen for presentation to T cells
D. Specific antigen binding in response to B-cell activation to promote neutralization and precipitation

4. Rheumatic fever develops due to an autoimmune process. Which of the following mechanisms of autoimmunity is primarily responsible for the development of rheumatic fever?

A. Endocrine abnormalities
B. Increased B-cell function

4. (Continued)
C. Intrinsic cytokine imbalance
D. Increased T-cell help due to cytokine stimulation
E. Molecular mimicry

5. Which of the following autoantibodies is least likely to be present in a patient with systemic lupus erythematosus?

A. Anti-dsDNA
B. Antinuclear antibodies
C. Anti-La (SS-B)
D. Antiphospholipid
E. Antierythrocyte

6. A 23-year-old woman is evaluated by her primary care physician because she is concerned that she may have systemic lupus erythematosus after hearing a public health announcement on the radio. She has no significant past medical history, and her only medication is occasional ibuprofen. She is not sexually active and works in a grocery store. She reports that she has had intermittent oral ulcers and right knee pain. Physical examination shows no evidence of alopecia, skin rash, or joint swelling/inflammation. Her blood work shows that she has a positive antinuclear antibody (ANA) at a titer of 1:40, but no other abnormalities. Which of the following statements is true?

A. Four diagnostic criteria are required to be diagnosed with systemic lupus erythematosus; this patient has three.
B. Four diagnostic criteria are required to be diagnosed with systemic lupus erythematosus; this patient has two.
C. If a urinalysis shows proteinuria, she will meet criteria for systemic lupus erythematosus.
D. She meets criteria for systemic lupus erythematosus because she has three criteria for disease.
E. T e demonstration of a positive ANA alone is adequate to diagnose systemic lupus erythematosus.

*Questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Principles *of* Internal Medicine Self-Assessment and Board Review. 19th ed. New York: McGraw-Hill; 2017.

7. A 32-year-old woman with long-standing diagnosis of systemic lupus erythematosus is evaluated by her rheumatologist as routine follow-up. A new cardiac murmur is heard and an echocardiogram is ordered. She is feeling well and has no fevers, weight loss, or preexisting cardiac disease. A vegetation on the mitral valve is demonstrated. Which of the following statements is true?

A. Blood cultures are unlikely to be positive.
B. Glucocorticoid therapy has been proven to lead to improvement in this condition.
C. Pericarditis is frequently present concomitantly.
D. T e lesion has a low risk of embolization.
E. T e patient has been surreptitiously using injection drugs.

8. A 24-year-old woman is newly diagnosed with systemic lupus erythematosus. Which of the following organ system complications is she most likely to have over the course of her lifetime?

A. Cardiopulmonary
B. Cutaneous
C. Hematologic
D. Musculoskeletal
E. Renal

9. A 45-year-old African American woman with systemic lupus erythematosus (SLE) presents to the emergency department with complaints of headache and fatigue. Her prior manifestations of SLE have been arthralgias, hemolytic anemia, malar rash, and mouth ulcers, and she is known to have high titers of antibodies to double-stranded DNA. She currently is taking prednisone, 5 mg daily, and hydroxychloroquine, 200 mg daily. On presentation, she is found to have a blood pressure of 190/110 mmHg with a heart rate of 98 bpm. A urinalysis shows 25 red blood cells (RBCs) per high-power field with 2+ proteinuria. No RBC casts are identified. Her blood urea nitrogen is 88 mg/dL and creatinine is 2.6 mg/dL (baseline 0.8 mg/dL). She has not previously had renal disease related to SLE and is not taking nonsteroidal anti-inflammatory drugs. She denies any recent illness, decreased oral intake, or diarrhea. What is the most appropriate next step in the management of this patient?

A. Initiate cyclophosphamide, 500 mg/m^2 body surface area intravenously (IV), and plan to repeat monthly for 3–6 months.
B. Initiate hemodialysis.

9. (Continued)
C. Initiate high-dose glucocorticoid therapy (IV methylprednisolone, 1000 mg daily for 3 doses, followed by oral prednisone, 1 mg/kg daily) and mycophenolate mofetil, 2 g daily.
D. Initiate plasmapheresis.
E. Withhold all therapy until renal biopsy is performed.

10. A 27-year-old woman is admitted to the intensive care unit after recent delivery of a full-term infant 3 days prior. T e patient was found to have right hemiparesis and a blue left hand. Physical examination is also notable for livedo reticularis. Her laboratories were notable for a white blood cell (WBC) count of 10.2/μL, hematocrit of 35%, and platelet count of 13,000/μL. Her blood urea nitrogen (BUN) is 36 mg/dL and her creatinine is 2.3 mg/dL. Although this pregnancy was uneventful, the three prior pregnancies resulted in early losses. A peripheral smear shows no evidence of schistocytes. Which of the following laboratory studies will best confirm the underlying etiology of her presentation?

A. Anticardiolipin antibody panel
B. Antinuclear antibody
C. Doppler examination of her left arm arterial tree
D. Echocardiography
E. Magnetic resonance imaging (MRI) of her brain

11. A 28-year-old woman comes to the emergency department complaining of 1 day of worsening right leg pain and swelling. She drove in a car 8 hours back from a hiking trip 2 days ago and then noticed some pain in the leg. At first she thought it was due to exertion, but it has worsened over the day. Her only past medical history is related to difficulty getting pregnant, with two prior spontaneous abortions. Her physical examination is notable for normal vital signs, heart, and lung examination. Her right leg is swollen from the mid-thigh down and is tender. Doppler studies demonstrate a large deep venous thrombosis in the femoral and ileac veins extending into the pelvis. Laboratory studies on admission prior to therapy show normal electrolytes, normal WBC and platelet counts, normal prothrombin time, and an activated partial thromboplastin time 3× normal. Her pregnancy test is negative. Low-molecular-weight heparin therapy is initiated in the emergency department. Subsequent therapy should include which of the following?

A. Rituximab 375 mg/m^2 per week for 4 weeks
B. Warfarin with international normalized ratio (INR) goal of 2.0–3.0 for 3 months

11. (Continued)
C. Warfarin with INR goal of 2.0–3.0 for 12 months
D. Warfarin with INR goal of 2.5–3.5 for life
E. Warfarin with INR goal of 2.5–3.5 for 12 months followed by daily aspirin for life

12. Patients with antiphospholipid syndrome will often falsely test positive for which of the following infectious diseases?

A. Malaria
B. Human immunodeficiency virus (HIV)
C. Schistosomiasis
D. Hepatitis C
E. Syphilis

13. Which of the following is the most frequent site of joint involvement in established rheumatoid arthritis?

A. Distal interphalangeal joint
B. Hip
C. Knee
D. Spine
E. Wrist

14. In patients with established rheumatoid arthritis, all of the following pulmonary radiographic findings may be explained by their rheumatologic condition EXCEPT:

A. Bilateral interstitial infiltrates
B. Bronchiectasis
C. Lobar infiltrate
D. Solitary pulmonary nodule
E. Unilateral pleural ef usion

15. Which of the following is the earliest plain radiographic finding of rheumatoid arthritis?

A. Juxta-articular osteopenia
B. No abnormality
C. Soft tissue swelling
D. Subchondral erosions
E. Symmetric joint space loss

16. All of the following are characteristic extra-articular manifestations of rheumatoid arthritis EXCEPT:

A. Anemia
B. Cutaneous vasculitis
C. Pericarditis
D. Secondary Sjögren syndrome
E. T rombocytopenia

17. All of the following agents have been shown to have disease-modifying antirheumatic drug (DMARD) efficacy in patients with rheumatoid arthritis EXCEPT:
A. Infliximab
B. Leflunomide
C. Methotrexate
D. Naproxen
E. Rituximab

18. All of the following are characteristics of Felty syndrome EXCEPT:

A. Neutropenia
B. Nodular rheumatoid arthritis
C. Occurs in the late stages of rheumatoid arthritis
D. Splenomegaly
E. T rombocytopenia

19. Which of the following malignancies are patients with rheumatoid arthritis specifically at higher risk for?

A. Colon cancer
B. Lung cancer
C. Lymphoma
D. Melanoma
E. Glioblastoma multiforme

20. Which of the following is the most common clinical presentation of acute rheumatic fever?

A. Carditis
B. Chorea
C. Erythema marginatum
D. Polyarthritis
E. Subcutaneous nodules

21. A 19-year-old recent immigrant from Ethiopia comes to your clinic to establish primary care. She currently feels well. Her past medical history is notable for a recent admission to the hospital for new-onset atrial fibrillation. As a child in Ethiopia, she developed an illness that caused uncontrolled flailing of her limbs and tongue lasting approximately 1 month. She also has had three episodes of migratory large-joint arthritis during her adolescence that resolved with pills that she received from the pharmacy. She is currently taking metoprolol and warfarin and has no known drug allergies. Physical examination reveals an irregularly irregular heart beat with normal blood pressure. Her point of maximal impulse (PMI) is most prominent at the midclavicular line and is normal in size. An early diastolic rumble and 3/6 holosystolic

21. (Continued)
murmur are heard at the apex. A soft early diastolic murmur is also heard at the left third intercostal space. You refer her to a cardiologist for evaluation of valve replacement and echocardiography. What other intervention might you consider at this time?

A. Daily aspirin
B. Daily doxycycline
C. Low-dose glucocorticoids
D. Monthly penicillin G injections
E. Penicillin G injections as needed for all sore throats

22. Most of the manifestations of acute rheumatic fever present approximately 3 weeks after the precipitating group A streptococcal infection. Which manifestation may present several months after the precipitating infection?

A. Chorea
B. Erythema marginatum
C. Fever
D. Polyarthritis
E. Subcutaneous nodules

23. A patient with a diagnosis of scleroderma who has dif use cutaneous involvement presents with malignant hypertension, oliguria, edema, hemolytic anemia, and renal failure. You make a diagnosis of scleroderma renal crisis. Which of the following is the recommended treatment?

A. Captopril
B. Carvedilol
C. Clonidine
D. Diltiazem
E. Nitroprusside

24. Which of the following is nearly twice as common in patients with dif use cutaneous systemic sclerosis than in limited cutaneous systemic sclerosis?

A. Esophageal involvement
B. Pulmonary arterial hypertension
C. Pulmonary fibrosis
D. Raynaud phenomenon
E. Skin involvement

25. Which of the following autoantibodies is typically present in high titers in patients with mixed connective tissue disease?

A. Anticentromere
B. Anti-La
C. Anti-Ro
D. Anti–Scl-70
E. Anti–U1-RNP

26. A 57-year-old woman with depression and chronic migraine headaches reports several years of dry mouth and dry eyes. Her primary complaint is that she can no longer eat her favorite crackers, although she does report photosensitivity and eye burning on further questioning. She has no other associated symptoms. Examination shows dry, erythematous, sticky oral mucosa. All of the following tests are likely to be positive in this patient EXCEPT:

A. La/SS-B antibody
B. Ro/SS-A antibody
C. Schirmer I test
D. Scl-70 antibody
E. Sialometry

27. A patient with primary Sjögren syndrome that was diagnosed 6 years ago and treated with tear replacement for symptomatic relief notes continued parotid swelling for the last 3 months. She has also noted enlarging posterior cervical lymph nodes. Evaluation shows leukopenia and low C4 complement levels. What is the most likely diagnosis?

A. Amyloidosis
B. Chronic pancreatitis
C. HIV infection
D. Lymphoma
E. Secondary Sjögren syndrome

28. Which of the following is the most common extraglandular manifestation of primary Sjögren syndrome?

A. Arthralgias/arthritis
B. Lymphoma
C. Peripheral neuropathy
D. Raynaud phenomenon
E. Vasculitis

29. A 43-year-old Japanese woman presents to your clinic with 6 months of dry irritated eyes, dry mouth, and cheek swelling. On examination, she has parotic gland enlargement bilaterally. Sialometry is abnormal. Biopsy of the minor salivary glands in the lip shows granulomatous inflammation. Serologies show a negative SS-A and SS-B antibodies. Which of the following is the most likely diagnosis?

29. (Continued)
A. Systemic sclerosis
B. Sarcoidosis
C. Sjögren syndrome
D. HIV-associated sicca syndrome
E. Eosinophilic granulomatosis with polyangiitis

30. Histocompatibility antigen HLA-B27 is present in what percentage of North American patients with ankylosing spondylitis?

A. 10%
B. 30%
C. 50%
D. 90%
E. 100%

31. Which of the following is the most common extra-articular manifestation of ankylosing spondylitis?

A. Anterior uveitis
B. Aortic insufficiency
C. Inflammatory bower disease
D. Pulmonary fibrosis
E. T ird-degree heart block

32. A 25-year-old man is seeing his primary care physician for evaluation of low back pain. T e pain is severe, worse in the morning, improved with exercise, and worse with rest; in particular, nighttime sleeping is difficult. He does feel quite stif in the morning for at least 30 minutes. An MRI of his lower back is obtained and shows active inflammation in the sacroiliac joint. On further questioning, he reports a history of unilateral eye redness treated with glucocorticoids about 2 years ago. A test for HLA-B27 is positive. Which of the following is first-line therapy for his condition?

A. Infliximab
B. Naproxen
C. Prednisone
D. Rituximab
E. Tramadol

33. A 27-year-old man is seen at his primary care physician's office for evaluation of painful arthritis involving the right knee associated with dif use bilateral finger swelling. He is otherwise healthy but does recall a severe bout of diarrheal illness about 3–4 weeks prior that spontaneously resolved. He works as a recreation supervisor at a daycare center and said many of the children had a similar diarrheal illness. He takes no medications and reports rare marijuana use.

33. (Continued)
On review of systems, he reports painful urination. Examination shows inflammatory arthritis of the right knee, dactylitis, and normal genitourinary examination. He is diagnosed with reactive arthritis. Which of the following was the most likely etiologic agent of his diarrhea?
A. Campylobacter jejuni
B. Clostridium di*ffi*cile
C. Escherichia coli
D. Helicobacter pylori
E. Shigella f exneri

34. Which of the following statements regarding the arthritis of Whipple disease is true?

A. Arthritis is a rare finding in Whipple disease.
B. Joint manifestations are usually concurrent with gastrointestinal symptoms and malabsorption.
C. Radiography frequently shows joint erosions.
D. Synovial fluid examination is unlikely to show polymorphonuclear cells.
E. None of the above.

35. Which of the following definitions best fits the term enthesitis?

A. A palpable vibratory or crackling sensation elicited with joint motion
B. Alteration of joint alignment so that articulating surfaces incompletely approximate each other
C. Inflammation at the site of tendinous or ligamentous insertion into bone
D. Inflammation of the periarticular membrane lining the joint capsule
E. Inflammation of a saclike cavity near a joint that decreases friction

36. All of the following help distinguish psoriatic arthritis from other joint disorders EXCEPT:

A. Dactylitis
B. Enthesitis
C. Nail pitting
D. Presence of diarrhea
E. Shortening of digits

37. Which cardiac valvular lesion is most common in patients with ankylosing spondylitis?

A. Aortic regurgitation
B. Mitral regurgitation
C. Mitral stenosis
D. Pulmonic stenosis
E. Tricuspid regurgitation

38. All of the following vasculitic syndromes are thought to be due to immune complex deposition EXCEPT:

A. Cryoglobulinemic vasculitis
B. Granulomatosis with polyangiitis
C. IgA vasculitis (Henoch-Schönlein)
D. Polyarteritis nodosa associated with hepatitis B
E. Serum sickness

39. A 40-year-old male presents to the emergency department with 2 days of low-volume hemoptysis. He reports that he has been coughing up 2–5 tablespoons of blood each day. He does report mild chest pain, low-grade fevers, and weight loss. In addition, he has had about 1 year of severe upper respiratory symptoms including frequent epistaxis and purulent discharge treated with several courses of antibiotics. Aside from mild hyperlipidemia, he is otherwise healthy. His only medications are daily aspirin and lovastatin. On physical examination, he has normal vital signs and upper airway is notable for saddle nose deformity and clear lungs. A computed tomography (CT) of the chest shows multiple cavitating nodules and urinalysis shows red blood cells. Which of the following tests of ers the highest diagnostic yield to make the appropriate diagnosis?

A. Deep skin biopsy
B. Percutaneous kidney biopsy
C. Pulmonary angiogram
D. Surgical lung biopsy
E. Upper airway biopsy

40. An 84-year-old woman is seen by her primary care physician for evaluation of severe headaches. She noted these several weeks ago, and they have been getting worse. Although she has not had any visual aura, she is concerned that she has been intermittently losing vision in her left eye for the last few days. She denies new weakness or numbness, but she does report jaw pain with eating. Her past medical history includes coronary artery disease requiring a bypass grafting 10 years prior, diabetes mellitus, hyperlipidemia, and mild depression. Full review of symptoms is notable for night sweats and mild low back pain particularly prominent in the morning. Which of the following is the next most appropriate step?

A. Aspirin 975 mg orally daily
B. Measurement of erythrocyte sedimentation rate
C. Immediate initiation of glucocorticoids
D. Referral for temporal artery biopsy
E. Referral for ultrasound of temporal artery

41. A 54-year-old man is evaluated for cutaneous vasculitis and peripheral nephropathy. Because of concomitant renal dysfunction, he undergoes kidney biopsy that shows glomerulonephritis. Cryoglobulins are demonstrated in the peripheral blood. Which of the following laboratory studies should be sent to determine the etiology?

A. Hepatitis B surface antigen
B. Antineutrophil cytoplasmic antibody (ANCA)
C. Hepatitis C polymerase chain reaction
D. HIV antibody
E. Rheumatoid factor

42. An 18-year-old man is admitted to the hospital with acute onset of crushing substernal chest pain that began abruptly 30 minutes ago. He reports the pain radiating to his neck and right arm. He has otherwise been in good health. He currently plays trumpet in his high school marching band but does not participate regularly in aerobic activities. On physical examination, he is diaphoretic and tachypneic. His blood pressure is 100/48 mmHg and heart rate is 110 bpm. His cardiovascular examination has a regular rhythm but is tachycardic. A 2/6 holosystolic murmur is heard best at the apex and radiates to the axilla. His lungs have bilateral rales at the bases. T e electrocardiogram demonstrates 4 mm of ST elevation in the anterior leads. On further questioning regarding his past medical history, he recalls having been told that he was hospitalized for some problem with his heart when he was 2 years old. His mother, who accompanies him, reports that he received aspirin and γ-globulin as treatment. Since that time, he has required intermittent follow-up with echocardiography. What is the most likely cause of this patient's acute coronary syndrome?

A. Dissection of the aortic root and left coronary ostia
B. Presence of a myocardial bridge overlying the left anterior descending artery
C. T rombosis of a coronary artery aneurysm
D. Vasospasm following cocaine ingestion
E. Vasculitis involving the left anterior descending artery

43. You are seeing in follow-up a 46-year-old man who, 6 months ago, presented to the hospital acutely with hemoptysis, dif use nodular pulmonary infiltrates, and glomerulonephritis. Workup revealed a positive serologic study for antibodies against cytoplasmic ANCA and he was eventually diagnosed with granulomatosis with polyangiitis. Treatment was initiated with high-dose glucocorticoids and daily cyclophosphamide with excellent clinical response.

43. (Continued)
You are ready today to have the patient transition from induction therapy with cyclophosphamide to maintenance therapy with azathioprine. What blood test should you check before starting azathioprine?

A. ANCA titers
B. Cryoglobulins
C. CYP3A4 genotyping
D. Glucose-6-phosphate dehydrogenase enzyme levels
E. T iopurine methyltransferase enzyme activity

44. All of the following vascular beds are typically af ected by polyarteritis nodosa EXCEPT:

A. Cerebral arteries
B. Coronary arteries
C. Pulmonary arteries
D. Renal arteries
E. Splanchnic arteries

45. Lung biopsy has the greatest diagnostic yield in which of the following vasculitic syndromes?

A. Cryoglobulinemic vasculitis
B. Cutaneous vasculitis
C. Granulomatosis with polyangiitis (Wegener's)
D. IgA vasculitis (Henoch-Schönlein)
E. Polyarteritis nodosa

46. In a patient with suspected granulomatosis with polyangiitis (Wegener's), which of the following lung radiologic findings is least likely?

A. Bronchiectasis
B. Endobronchial stenosis
C. Multiple cavitating nodules
D. Nodular infiltrates
E. Solitary cavitating nodule

47. Which of the following is required for the diagnosis of Behçet's disease?

A. Large-vessel vasculitis
B. Pathergy test
C. Recurrent oral ulceration
D. Recurrent genital ulceration
E. Uveitis

48. A 25-year-old woman presents with a complaint of painful mouth ulcerations. She describes these lesions as shallow ulcers that last for 1 or 2 weeks. T e ulcers have been appearing for the last 6 months. For the last 2 days, the patient has had a painful red eye. She has had no genital ulcerations, arthritis, skin rashes, or

48. (Continued)
photosensitivity. On physical examination, the patient appears well developed and in no distress. She has a temperature of 37.6°C (99.7°F), heart rate of 86 bpm, blood pressure of 126/72 mmHg, and respiratory rate of 16 bpm. Examination of the oral mucosa reveals two shallow ulcers with a yellow base on the buccal mucosa. T e ophthalmologic examination is consistent with anterior uveitis. T e cardiopulmonary examination is normal. She has no arthritis, but medially on the right thigh, there is a palpable cord in the saphenous vein. Laboratory studies reveal an erythrocyte sedimentation rate of 68 seconds. WBC count is 10,230/μL with a dif erential of 68% polymorphonuclear cells, 28% lymphocytes, and 4% monocytes. T e antinuclear antibody and anti-dsDNA antibody are negative. C3 is 89 mg/dL and C4 is 24 mg/dL. What is the most likely diagnosis?

A. Behçet's disease
B. Bullous pemphigoid
C. Discoid lupus erythematosus
D. Sjögren syndrome
E. Systemic lupus erythematosus

49. All of the following are known complications of Behçet's disease EXCEPT:

A. Arterial thrombosis
B. Central nervous system involvement
C. Deep vein thrombosis
D. Pulmonary artery vasculitis
E. All of the above are known complications of Behçet's syndrome

50. An elevation in which of the following serum enzymes is the most sensitive indicator of myositis?

A. Aldolase
B. Creatinine kinase
C. Glutamic-oxaloacetic transaminase
D. Glutamate pyruvate transaminase
E. Lactate dehydrogenase

51. A 64-year-old woman is evaluated for weakness. She has had several weeks of difficulty brushing her teeth and combing her hair. She has also noted a rash on her face. Examination is notable for a heliotrope rash and proximal muscle weakness. Serum creatinine kinase (CK) is elevated and she is diagnosed with dermatomyositis. After evaluation by a rheumatologist, she is found to have anti-Jo-1 antibodies. She is also likely to have which of the following findings?

51. (Continued)

A. Ankylosing spondylitis
B. Inflammatory bowel disease
C. Interstitial lung disease
D. Primary biliary cirrhosis
E. Psoriasis

52. A 63-year-old woman is evaluated for a rash on her eyes and fatigue for 1 month. She reports difficulty with arm and leg strength and constant fatigue, but no fevers or sweats. She also has noted that she has a red discoloration around her eyes. She has hypothyroidism but is otherwise well. On examination, she has a heliotrope rash and proximal muscle weakness. A diagnosis of dermatomyositis is made after demonstration of elevated serum creatinine kinase and confirmatory electromyograms. Which of the following studies should be performed as well to look for associated conditions?

A. Mammogram
B. Serum antinuclear antibody measurement
C. Stool examination for ova and parasites
D. T yroid-stimulating immunoglobulins
E. Titers of antibodies to varicella-zoster

53. You are seeing your long-term patient today. He has a history of coronary artery disease, suf ering a lateral myocardial infarction 1 year ago. At that time, he was started on simvastatin, aspirin, metoprolol, and lisinopril. About 2 months ago, he started noting thigh and shoulder soreness. One month after onset, his muscle pain had increased and he was noticing weakness. His CK was elevated to 8× the upper limit of normal. His simvastatin was discontinued 3 weeks ago. Today, he reports that his pain has continued and, if anything, is worse than a month ago. His CK is 12× the upper limit of normal. What is the next best test to establish a diagnosis?

A. Antibody against 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR)
B. Antinuclear antibody (ANA)
C. Anti-Jo-1 antibody
D. Antibody against signal recognition particle (SRP)
E. Aldolase levels

54. A 47-year-old man is evaluated for 1 year of recurrent episodes of bilateral ear swelling. T e ear is painful during these events, and the right ear has become floppy. He is otherwise healthy and reports no illicit habits. He works in an office, and his only sport is tennis. On examination, the left ear has a

54. (Continued)

beefy red color and the pinna is tender and swollen; the earlobe appears minimally swollen but is neither red nor tender. Which of the following is the most likely explanation for this finding?

A. Behçet's disease
B. Cogan's syndrome
C. Hemoglobinopathy
D. Recurrent trauma
E. Relapsing polychondritis

55. All of the following have been implicated in the proposed pathogenesis of sarcoidosis EXCEPT:

A. Exposure to mold
B. Genetic susceptibility
C. Immune response to mycobacterial proteins
D. Infection with Propionibacterium acnes
E. Malignant expansion of helper T cells

56. Which of the following statements regarding pulmonary sarcoidosis is true?

A. Lung involvement is the second most common manifestation of sarcoidosis, behind only cutaneous involvement.
B. Obstructive disease is a rare manifestation of pulmonary sarcoidosis.
C. Pulmonary hypertension never responds to therapy in sarcoidosis patients.
D. Pulmonary infiltrates in sarcoidosis tend to be predominantly an upper lobe process.
E. T e presence of cough should prompt evaluation for a cause other than pulmonary sarcoidosis.

57. You are seeing a 55-year-old white man with a history of sarcoidosis. He ran out of prednisone about 2 months prior to seeing you and, except for some constipation, feels well. A metabolic panel reveals a calcium of 12.2 mg/dL (normal up to 10.5 mg/dL). You know that sarcoidosis can be associated with hypercalcemia. Which of the following is the correct mechanism for sarcoidosis-associated hypercalcemia?

A. Direct granulomatous involvement of the axial skeleton causing calcium release from bones
B. Direct stimulation of increased intestinal calcium absorption
C. Increased parathyroid hormone production
D. Increased production of 1,25-dihydroxyvitamin D
E. Increased production of 25-hydroxyvitamin D

58. In which population is cardiac sarcoidosis most common?

A. African American
B. East European
C. Japanese
D. South American
E. Australian

59. Which of the following is a potential cardiac manifestation of sarcoidosis?

A. Dilated cardiomyopathy
B. Heart block
C. Valvular stenosis
D. Ventricular tachyarrhythmias
E. All of the above

60. You are rounding on a 34-year-old man who presented to you with unexplained pancreatitis 2 weeks ago. Imaging of his pancreas showed dif use pancreatic enlargement. He denies any alcohol intake and did not have any gallstones on imaging. Interestingly, on examination, he also has marked lacrimal gland and submandibular gland enlargement. Biopsy of his submandibular gland is shown in **Figure 1**. T e cells shown in the figure stained strongly positive for IgG4, CD19, and CD138. Which of the following is the appropriate therapy?

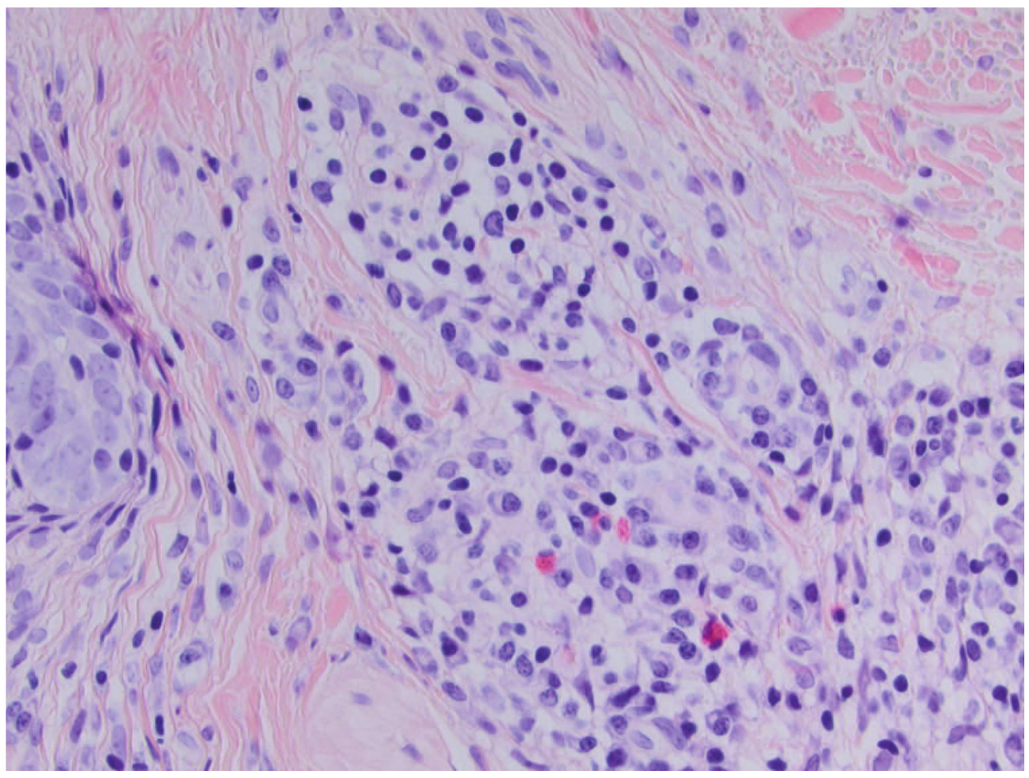


FIGURE 1

A. T alidomide and dexamethasone
B. Cytomegalovirus (CMV) immunoglobulin and ganciclovir
C. Systemic chemotherapy
D. Prednisone
E. Anakinra

61. You are seeing a 19-year-old woman today in consultation for recurrent fevers. She reports several years of fevers, occurring on average every 2–3 months. T ese episodes are unpredictable, although she thinks they may occur in times of psychological stress. Each febrile episode lasts 2–3 days. She also has recurrent episodes of abdominal pain. Repeated blood cultures have been negative, even during acute febrile episodes. Similarly, abdominal CT scans have shown no obvious etiology for her pain. During one episode, she underwent an exploratory laparotomy, which showed peritoneal adhesions and a sterile neutrophilic peritoneal exudate. She also notes that when she exercises, she develops intense muscle pains that last for days. An extensive serologic search for autoantibodies returned negative including antinuclear antibodies. Which of the following is the most likely diagnosis?

A. Familial Mediterranean fever
B. Lymphoma
C. Relapsing fever
D. Subacute bacterial endocarditis
E. Systemic lupus erythematosus

62. You are seeing a 19-year-old woman whom you just diagnosed with familial Mediterranean fever. Which of the following medications would you prescribe to reduce attacks and help prevent the development of systemic amyloidosis?

A. Colchicine
B. Cyclosporine
C. Diflunisal
D. Prednisone
E. T alidomide

63. Which of the following joints is often spared by osteoarthritis?

A. Cervical spine
B. Distal interphalangeal joint
C. Hip
D. Proximal interphalangeal joint
E. Wrist

64. Which of the following statements regarding osteoarthritis is true?

A. During the diagnostic workup of a suspected osteoarthritic joint, MRI is warranted to evaluate for any other causes.
B. Loss of cartilage causes pain due to direct stimulation of pain receptors in joint cartilage itself.

64. (Continued)

C. Osteoarthritis is the second most common cause of arthritis, behind rheumatoid arthritis.
D. Synovial fluid white blood cell count is usually less than 1000 cells/μL in osteoarthritis.
E. T e severity of radiographic changes in osteoarthritis correlates well with symptoms.

65. You are seeing a 60-year-old obese woman with bilateral knee osteoarthritis. She describes pain most days and limiting pain at least 2 days/week. She has tried activity modification (walking less) without success. All of the following therapies have been shown to be efficacious in treating osteoarthritis symptoms EXCEPT:

A. Acetaminophen
B. Glucocorticoid intra-articular injections
C. Glucosamine-chondroitin
D. Naproxen
E. Total joint arthroplasty

66. You are seeing a 72-year-old man with only a history of hypertension on hydrochlorothiazide. He presents today with acute, excruciating knee pain. On examination, his knee is warm, mildly erythematous, swollen, and tender to the touch or passive movement. Microscopic examination of joint fluid is shown in **Figure 2**. What is his most likely metabolic derangement?

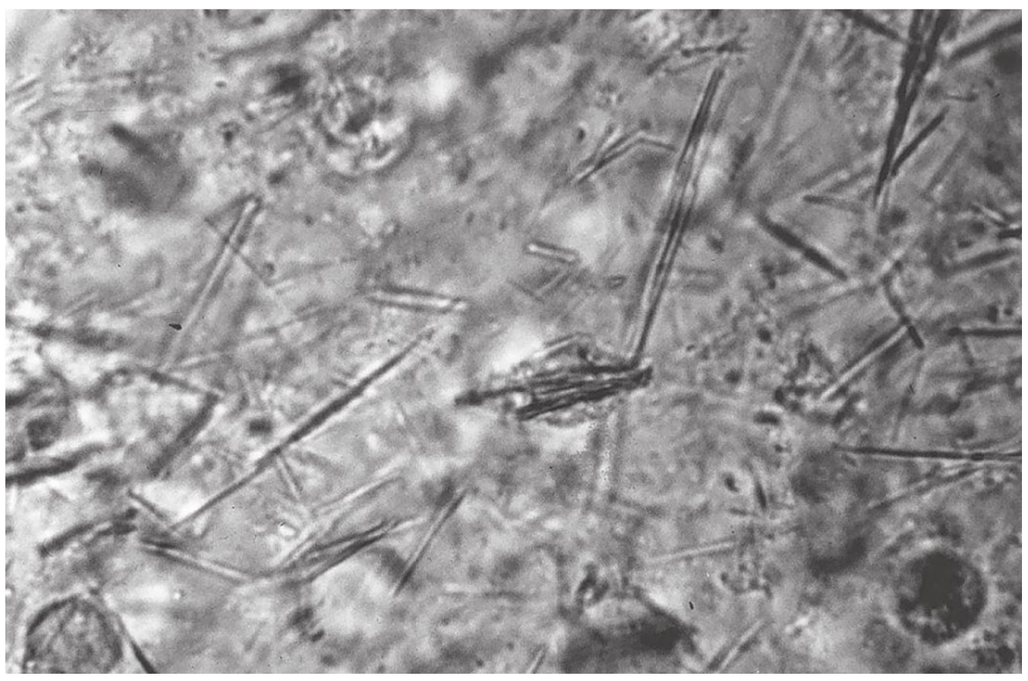


FIGURE 2

A. Acute bacterial joint infection
B. Antibodies to antinuclear antigens
C. Hyaline cartilage degeneration
D. Increased production of inorganic pyrophosphate
E. Uric acid overproduction

67. You are planning on starting allopurinol for a new diagnosis of gouty arthritis. Which of the following best describes appropriate dosing strategies for allopurinol?

A. Allopurinol and azathioprine are commonly used together in the treatment of gout.
B. Allopurinol dosing should be adjusted for liver function.
C. Allopurinol dosing should be titrated to achieve a serum uric acid level less than 6 mg/dL.
D. Allopurinol should be avoided when patients are taking colchicine.
E. Allopurinol toxicity is more common in patients expressing HLA-B27.

68. A 42-year-old woman is seen in her primary care doctor's office complaining of dif use pains and fatigue. She has a difficult time localizing the pain to any particular joint or location, but reports it af ects her upper and lower extremities, neck, and hips. It is described as achy and 10 out of 10 in intensity. She feels that her joints are stif but does not notice that it is worse in the morning. T e pain has been present for the past 6 months and is increasing in intensity. She has tried both over-the-counter ibuprofen and acetaminophen without significant relief. T e patient feels as if the pain is interfering with her ability to get restful sleep and is making it difficult for her to concentrate. She has missed multiple days of work as a waitress and fears that she will lose her job. T ere is a medical history of depression and obesity. T e patient currently is taking venlafaxine-sustained release 150 mg daily. She has a family history of rheumatoid arthritis in her mother. She smokes one pack of cigarettes daily. On physical examination, vital signs are normal. Body mass index is 36 kg/m^2. Joint examination demonstrates no erythema, swelling, or ef usions. T ere is dif use pain with palpation at the insertion points of the suboccipital muscles, at the midpoint of the upper border of the trapezius muscle, along the second costochondral junction, at the lateral epicondyles, and along the medial fat pad of the knees. All of the following statements regarding the cause of this patient's dif use pain syndrome are true EXCEPT:

A. Cognitive dysfunction, sleep disturbance, anxiety, and depression are common comorbid neuropsychological conditions.
B. Pain in this syndrome is associated with increased evoked pain sensitivity.

68. (Continued)

C. Pain in this syndrome is often localized to specific joints.
D. T is syndrome is present in 2–5% of the general population, but increases in prevalence to 20% or more of patients with degenerative or inflammatory rheumatic disorders.
E. Women are nine times more likely than men to be af ected by this syndrome.

69. A 36-year-old woman presents to your office with dif use pain throughout her body associated with fatigue, insomnia, and difficulty concentrating. She finds the pain difficult to localize but reports that it is 7–8 out of 10 in intensity and not relieved by nonsteroidal anti-inflammatory medications. She has a long-standing history of generalized anxiety disorder and is treated with sertraline 100 mg daily as well as clonazepam 1 mg twice daily. On examination, she has pain with palpation at several musculoskeletal sites. Her laboratory examination demonstrates a normal complete blood count, basic metabolic panel, erythrocyte sedimentation rate, and rheumatoid factor. You diagnose her with fibromyalgia. All of the following therapies are recommended as part of the treatment plan for fibromyalgia EXCEPT:

A. An exercise program that includes strength training, aerobic exercise, and yoga
B. Cognitive-behavioral therapy for insomnia
C. Milnacipran
D. Oxycodone
E. Pregabalin

70. A 53-year-old woman presents to your clinic complaining of fatigue and generalized pain that have worsened over 2 years. She also describes irritability and poor sleep and is concerned that she is depressed. She reveals that she was recently separated from her husband and has been stressed at work. Which of the following elements in her history and physical examination would meet American College of Rheumatology criteria for diagnosis of fibromyalgia?

A. Dif use chronic pain and abnormal sleep
B. Dif use pain without other etiology and evidence of major depression
C. Major depression, life stressor, chronic pain, and female sex
D. Major depression and pain on palpation at 6 of 18 tender point sites
E. Widespread chronic pain and pain on palpation at 11 of 18 tender point sites

71. A 42-year-old man is found to have the following finding on a physical examination (**Figure 3**). All of the following conditions are associated with this finding EXCEPT:



FIGURE 3
Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, © 1991, 1995. Used by permission of the American College of Rheumatology.)

A. Chronic obstructive pulmonary disease
B. Cyanotic congenital heart disease
C. Cystic fibrosis
D. Hepatocellular carcinoma
E. Hyperthyroidism

72. A 52-year-old man presented to his primary care physician complaining of new-onset pain in the knuckles of his index and middle fingers of both hands. On examination, the second and third metacarpophalangeal (MCP) joints of both hands are swollen and tender. T e rest of his physical examination is normal. His past medical history is only notable for hyperlipidemia controlled with atorvastatin. His laboratory studies are notable for an elevated ferritin, and after demonstration of a mutation of the HFE gene, he is diagnosed with hemochromatosis. Which of the following statements regarding his joint abnormalities is true?

A. T e second and third finger MCPs are also typically involved in osteoarthritis.
B. Arthropathy is unlikely related to hemochromatosis.
C. Arthropathy may progress with phlebotomy.
D. Arthropathy occurs in less than 20% of patients with hemochromatosis.
E. Radiographs are likely to show erosions in the MCPs.

73. A 64-year-old woman is seen by her primary care physician complaining of hip pain for about 1 week. She localizes the pain to the lateral aspect of

73. (Continued)
her right hip and describes it as sharp. It is worse with movement and she finds it difficult to lie on her right side. T e pain began soon after the patient was planting her garden. She has a medical history of obesity, osteoarthritis of the knees, and hypertension. Her medications include losartan 50 mg daily and hydrochlorothiazide 25 mg daily. For the pain, she has taken ibuprofen 600 mg as needed with mild to moderate relief of pain. On physical examination, the patient is not febrile and her vital signs are unremarkable. On examination of the hip, pain is elicited with external rotation and resisted abduction of the hip. Direct palpation over the lateral aspect of the upper portion of the femur near the hip joint reproduces the pain. What is the most likely diagnosis in this patient?

A. Avascular necrosis of the hip
B. Iliotibial band syndrome
C. Meralgia paresthetica
D. Septic arthritis
E. Trochanteric bursitis

74. A 32-year-old woman is seen in clinic with a complaint of left knee pain. She enjoys running long distances and is currently training for a marathon. She is running on average 30–40 miles weekly. She currently is experiencing an aching pain on the lateral aspect of her left knee. T ere is a burning sensation that also continues up the lateral aspect of her thigh. She denies any injury to her knee, and she has not felt that it was hot or swollen. She is otherwise healthy and takes no medications other than herbal supplements. Physical examination of the knee reveals point tenderness over the lateral femoral condyle that is worse with flexing the knee. T e patient is asked to lie on her right side with her right knee and hip flexed at 90 degrees. Her left leg is extended at the hip and slowly lowered into adduction behind the bottom leg, reproducing the patient's left knee pain. All of the following treatments can be recommended for this patient EXCEPT:

A. Assessment of the patient's running shoes to ensure a proper fit
B. Glucocorticoid injection so as not to interfere with the patient's continued preparation for the upcoming marathon
C. Ibuprofen 600–800 mg every 6 hours as needed for pain
D. Referral for physical therapy
E. Referral for surgical release if conservative therapy fails

75. A 58-year-old woman presents complaining of right shoulder pain. She does not recall any prior injury but notes that she feels that the shoulder has been getting progressively more stif over the last several months. She previously had several episodes of bursitis of the right shoulder that were treated successfully with nonsteroidal anti-inflammatory drugs and glucocorticoid injections. T e patient's past medical history is also significant for diabetes mellitus, for which she takes metformin and glyburide. On physical examination, the right shoulder is not warm or red but is tender to touch. Passive and active range of motion are limited in flexion, extension, and abduction. A right shoulder radiogram shows osteopenia without evidence of joint erosion or osteophytes. What is the most likely diagnosis?

A. Adhesive capsulitis
B. Avascular necrosis
C. Bicipital tendinitis
D. Osteoarthritis
E. Rotator cuf tear

76. A 32-year-old woman presents to clinic with right thumb and wrist pain that has worsened over several weeks. She has pain when she pinches her thumb against her other fingers. Her only other history is that she is a new mother with an 8-week-old infant at home. On physical examination, she has mild swelling and tenderness over the radial styloid process and pain is elicited when she places her thumb in her palm and grasps it with her fingers. A Phalen maneuver is negative. Which condition is most likely?
A. Carpal tunnel syndrome
B. De Quervain tenosynovitis
C. Gouty arthritis of the first metacarpophalangeal joint
D. Palmar fasciitis
E. Rheumatoid arthritis

77. You are evaluating a 42-year-old woman who complains of pain on the underside of her right heel that is excruciating in the morning when she first walks from bed to the bathroom. T e pain improves somewhat during the morning but again worsens mid-day particularly when climbing stairs. She has a past medical history of hypertension, smokes one pack per day of cigarettes, and works as a waitress at a diner. Medications include hydrochlorothiazide and oral contraceptives. Physical examination is unremarkable except for flat feet and focal tenderness on the bottom of the right heel. T ere is no tenderness at the ankle or calf and the diameters of the lower legs are equivalent. A radiograph of the right

77. (Continued)
heel and ankle shows only heel spurs. All of the following statements regarding her condition are true EXCEPT:

A. Heel spurs are not diagnostic.
B. Local glucocorticoid injection incurs a risk of plantar facial rupture.
C. Oral contraceptives and smoking are risk factors.
D. Orthotic shoe implants may be beneficial.
E. T e prognosis for improvement is good.

ANSWERS

1. The answer is A.
(Chap. 1) The innate immune system is phylogenetically the oldest form of immunologic defense system, inherited from invertebrates. This is defense system uses germline-encoded proteins to recognize pathogen-associated molecular patterns. Cells of the innate immune system include macrophages, dendritic cells, and natural killer lymphocytes. The critical components of the innate immune system include recognition by germline-encoded host molecules and recognition of key microbe virulence factors, but no recognition of self-molecules and of benign foreign molecules or microbes. Adaptive immunity is found only in vertebrate animals and is based on generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of recognizing diverse environmental antigens.

2. The answer is A.
(Chap. 1) Complement activity, which results from the sequential interaction of a large number of plasma and cell membrane proteins, plays an important role in the inflammatory response. The classic pathway of complement activation is initiated by an antibody-antigen interaction. The first complement component (C1, a complex composed of three proteins) binds to immune complexes with activation mediated by C1q. Active C1 then initiates the cleavage and concomitant activation of components C4 and C2. The activated C1 is destroyed by a plasma protease inhibitor termed C1 esterase inhibitor. This is molecule also regulates clotting factor XI and kallikrein. Patients with a deficiency of C1 esterase inhibitor may develop angioedema, sometimes leading to death by asphyxia. Attacks may be precipitated by stress or trauma. In addition to low antigenic or functional levels of C1 esterase inhibitor, patients with this autosomal dominant condition may have normal levels of C1 and C3 but low levels of C4 and C2. Danazol therapy produces a striking increase in the level of this important inhibitor and alleviates the symptoms in many patients. An acquired form of angioedema caused by a deficiency of C1 esterase inhibitor has been described in patients with autoimmune or malignant disease.

3. The answer is C.
(Chap. 2) The human major histocompatibility complex (MHC) genes are located on a 4-megabase region on chromosome 6. The major function of the MHC complex genes is to produce proteins that are important in developing immunologic specificity through their role in binding antigen for presentation to T cells. This process is nonspecific, and the ability of a human leukocyte antigen (HLA) molecule to bind to a particular protein depends on the molecular fit between the amino acid sequence of a particular protein and the corresponding domain on the MHC molecule. Once a peptide has bound, the MHC-peptide complex binds to the T-cell receptor, after which the T cell must determine if an immune response should be generated. If an antigen is similar to an endogenous protein, the potential antigen will be recognized as a self-peptide, and tolerance to the antigen will be continued. The MHC I and II complexes have been implicated in the development of many autoimmune diseases, which occur when T cells fail to recognize a peptide as a self-peptide and an immune response is allowed to develop. MHC I and II genes also play a major role in tissue compatibility for transplantation and are important in generating immune-mediated rejection. The other options listed as answers refer to functions of immunoglobulins. The variable region of the immunoglobulin is a B-cell–specific response to an antigen to promote neutralization of the antigen through agglutination and precipitation. The constant region of the immunoglobulin is able to nonspecifically activate the immune system through complement activation and promotion of phagocytosis by neutrophils and macrophages.

4. The answer is E.
(Chap. 3) Derangements of normal processes may predispose to the development of autoimmunity. In general, these abnormal responses require both an exogenous trigger, such as infection (bacterial or viral) or cigarette smoking, and the presence of endogenous abnormalities in the cells of the immune system. One of the best examples of autoreactivity and autoimmune disease resulting from molecular mimicry is rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins as well as with neuronal antigens. Deposition of these autoantibodies in the heart initiates an inflammatory response, whereas their penetration into the brain can result in Sydenham chorea. Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus, rheumatoid arthritis, celiac disease, and multiple sclerosis (**Table 1**).

TABLE 1

MECHANISMS OF AUTOIMMUNITY

I. Exogenous
  A. Molecular mimicry
  B. Superantigenic stimulation
  C. Microbial and tissue damage–associated adjuvanticity
II. Endogenous
  A. Altered antigen presentation
    1. Loss of immunologic privilege
    2. Presentation of novel or cryptic epitopes (epitope spreading)
    3. Alteration of self-antigen
    4. Enhanced function of antigen-presenting cells
      a. Costimulatory molecule expression
      b. Cytokine production
  B. Increased T-cell help
    1. Cytokine production
    2. Costimulatory molecules
  C. Increased B-cell function
    1. B-cell activating factor
    2. Costimulatory molecules
  D. Apoptotic defects or defects in clearance of apoptotic material
  E. Cytokine imbalance
  F. Altered immunoregulation
  G. Endocrine abnormalities

Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous circular raised patches with adherent keratotic scaling
Photosensitivity	Exposure to ultraviolet light causes rash
Oral ulcers	Oral and nasopharyngeal ulcers observed by a physician
Arthritis	Nonerosive arthritis of two or more peripheral joints with tenderness, swelling, or effusion
Serositis	Pleuritis or pericarditis
Renal disorder	Proteinuria >0.5 g/d or 3+ or cellular casts
Neurologic disorder	Seizures, psychosis
Hematologic disorder	Hemolytic anemia or leukopenia, lymphopenia, thrombocytopenia
Immunologic disorder	Anti-dsDNA, anti-Sm, and/or antiphospholipid, low serum complement, positive direct Coombs
Antinuclear antibodies (ANA)	Abnormal titer of ANA

5. The answer is C.
(Chap. 4) Antinuclear antibodies are nearly ubiquitous in patients with systemic lupus erythematosus (SLE), with demonstration in 90% of affected patients. There are many other antibodies that can be demonstrated. The next most common antibodies are anti-dsDNA and anti-histone. Anti-dsDNA is very specific to SLE and may correlate with disease activity, nephritis, and vasculitis. Antiphospholipid antibodies can be demonstrated in about half of affected patients, whereas the remainder is present in less than half of SLE cases. Antierythrocyte antibodies are present in approximately 60% of SLE cases and can be measured by a direct Coombs test. In contrast, anti-La antibodies directed against the 47-kDa protein complexes to hY RNA is rare, present only in 10% of cases of SLE. It is associated with a decreased risk for nephritis.

6. The answer is B.
(Chap. 4) There are well-published, diagnostic criteria for SLE. They include four or more of the following criteria from the table below.

The patient described does not meet the arthritis criteria; her only criteria are oral ulcers and weakly positive ANA.

7. The answer is A.
(Chap. 4) The patient has Libman-Sacks endocarditis associated with her SLE. This results in fibrinous endocarditis and can lead to valvular insufficiencies, most often mitral or aortic, or embolism. It is not generally found with concomitant pericarditis, although this is another common cardiac manifestation of systemic lupus erythematosus. Although glucocorticoids and anti-inflammatory therapies have no proven benefit in this condition, they are often used in conjunction with supportive care. Because Libman-Sacks endocarditis is a culture-negative endocarditis and is not thought to be due to microbial infection, blood cultures will not be positive.

8. The answer is D.
(Chap. 4) SLE is a multisystem disease with diverse organ involvement and multiple different manifestations within an organ system. The most common system to be involved is the musculoskeletal system, with 95% of patients having involvement, most commonly as arthralgias or myalgias. Arthritis is also common and is one of the diagnostic criteria for SLE. Cutaneous and hematologic disease occurs in approximately 80%–85% of patients. Neurologic and cardiopulmonary disease affects approximately

60% of patients, whereas renal and gastrointestinal disease occurs in less than 50% of cases.

9. T e answer is C.
(Chap. 4) T is patient is presenting with acute lupus nephritis with evidence of hematuria, proteinuria, and an acute rise in creatinine. Together with infection, nephritis is the most common cause of mortality in the first decade after diagnosis of SLE and warrants prompt immunosuppressive therapy. It is important to assess for other potentially reversible causes of acute renal insufficiency, but this patient is not otherwise acutely ill and is taking no medications that would cause renal failure. T e urinalysis shows evidence of active nephritis with hematuria and proteinuria. Even in the absence of red blood cell (RBC) casts, therapy should not be withheld to await biopsy results in someone with a known diagnosis of SLE with consistent clinical presentation and urinary findings. T is patient also has other risk factors known to predict the development of lupus nephritis, including high titers of anti-dsDNA and African American race. T e mainstay of treatment for any life-threatening or organ-threatening manifestation of SLE is high-dose systemic glucocorticoids. Addition of cytotoxic or other immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) is recommended to treat serious complications of SLE, but their ef ects are delayed for 3–6 weeks after initiation of therapy, whereas the ef ects of glucocorticoids begin within 24 hours. T us, these agents alone should not be used to treat acute serious manifestations of SLE. T e choice of cytotoxic agent is at the discretion of the treating physician. Cyclophosphamide in combination with glucocorticoid therapy has been demonstrated to prevent development of end-stage renal disease better than glucocorticoids alone. Likewise, mycophenolate also prevents development of end-stage renal disease in combination with glucocorticoids, and some studies suggest that African Americans have a greater response to mycophenolate than to cyclophosphamide. Plasmapheresis is not indicated in the treatment of lupus nephritis but is useful in cases of severe hemolytic anemia or thrombotic thrombocytopenic purpura associated with SLE. Finally, this patient has no acute indication for hemodialysis and, with treatment, may recover renal function.

10. T e answer is A.
(Chap. 5) T e patient has multiple clinical manifestations of arterial thrombosis in her hand and brain and likely had placental insufficiency in the three prior pregnancies, which makes the possibility of antiphospholipid antibody syndrome likely. In addition, she has evidence of acute kidney injury, suggesting multisystem disease. T rombocytopenia may be due to hemolytic anemia, but the absence of schistocytes makes it less likely that she has thrombotic thrombocytopenic purpura. Although magnetic resonance imaging (MRI) of her brain and extremity duplex may confirm the presence of thrombosis, these will not diagnose antiphospholipid antibody syndrome. An anticardiolipin antibody screening panel will look for evidence of antibodies directed against cardiolipin and β-2 glycoprotein I. Additional testing for lupus anticoagulant determined by clotting assays such as the Russel viper venom time, false-positive rapid plasma reagin (RPR), and the activated partial thromboplastin time (aPTT) may also be useful. ANA is likely to be positive given the common overlap with SLE, but is nonspecific.

11. T e answer is D.
(Chap. 5) T is patient has a typical presentation of antiphospholipid syndrome (APS) with a deep venous thrombosis, history of spontaneous abortion, and isolated elevated aPTT due to a lupus anticoagulant. Additional clinical features of APS involving the arterial or venous circulation include livedo reticularis (24%), pulmonary embolism (14%), stroke (20%), transient ischemic attack (10%), myocardial infarction (10%), migraine (20%), preeclampsia (10%), thrombocytopenia (30%), and autoimmune hemolytic anemia (10%). Laboratory criteria include demonstration of lupus anticoagulant (elevated aPTT that does not correct on mixing), in conjunction with the presence of anticardiolipin and/or anti-β-2 glycoprotein I on two occasions 3 month apart. After diagnosis of a thrombotic event due to APS, patients should receive warfarin for life with a goal international normalized ratio (INR) of 2.5–3.5 alone or in combination with daily aspirin. During pregnancy, patients should receive heparin plus aspirin. Patients who develop recurrent thrombosis while on ef ective anticoagulation may benefit from a 5-day infusion of IV γ-globulin or 4 weeks of rituximab therapy. T e optimal therapy for patients with APS without a thrombotic event is not known; however, daily aspirin (80 mg) protects patients with SLE and antiphospholipid antibodies from thrombotic events. Warfarin for 3 months with INR goal of 2.0–3.0 is recommended therapy for deep vein thrombosis (DVT) with a known reversible precipitating event.

Warfarin for 6–12 months with an INR goal of 2.0–3.0 is recommended therapy for first episode of idiopathic DVT.

12. The answer is E.
(Chap. 5) Patients with APS often possess antibodies recognizing Treponema pallidum PL/cholesterol complexes, which are detected as biologic false-positive serologic tests for syphilis (BFP-STS) and Venereal Disease Research Laboratory (VDRL) tests. If syphilis is suspected, a specific direct treponemal test, such as fluorescent treponemal antibody absorption (FTA-ABS) should be obtained.

13. The answer is E.
(Chap. 6) Once the disease process of rheumatoid arthritis is established, the most common joints of involvement are the wrists, metacarpophalangeal joints, and proximal interphalangeal joints. Distal interphalangeal joint involvement is rarely due to rheumatoid arthritis and more often due to coexisting osteoarthritis.

14. The answer is C.
(Chap. 6) There is potential involvement of multiple organ systems in rheumatoid arthritis (RA). The most common pulmonary complication is pleural effusion that is typically exudative and presents with chest pain and dyspnea. RA is associated with a form of diffuse interstitial lung disease that may present with dyspnea and bilateral interstitial infiltrates that may be so extensive as to develop into a honeycomb pattern. Pulmonary nodules associated with rheumatoid arthritis may be solitary or multiple. They often occur in conjunction with cutaneous nodules. Bronchiectasis and respiratory bronchiolitis may also be due to rheumatoid arthritis. Many of these manifestations respond to immunosuppressive therapy. Lobar infiltrate has not been described to be caused by RA and is more commonly caused by an acute infectious etiology, often as a complication of RA immunosuppressive therapy.

15. The answer is A.
(Chap. 6) Joint imaging is a critical tool for both diagnosis and monitoring of disease status in RA. Plain radiographs, because of their ready availability and ease of film comparison, are most commonly ordered. The earliest clinical sign of RA is juxta-articular osteopenia, although this may be difficult to appreciate on newer, digitized films. Other findings include soft tissue swelling, symmetric joint space loss, and subchondral erosions most frequently in the wrists, metacarpophalangeal and proximal interphalangeal joints, and metatarsophalangeal joint.

16. The answer is E.
(Chap. 6) Anemia is common in RA and parallels the degree of inflammation as measured by C-reactive protein or erythrocyte sedimentation rate (ESR). Felty syndrome, typically occurring in late-stage poorly controlled disease, is characterized by the triad of neutropenia, splenomegaly, and rheumatoid nodules. Rheumatoid vasculitis is not common and typically occurs in long-standing disease. It is associated with hypocomplementemia. The cutaneous signs are typical of vasculitic lesions with palpable purpura, digital infarcts, livedo reticularis, and ulcers. Clinical manifestations of pericarditis occur in 10% of patients with echocardiographic or autopsy findings in about half of those cases. Secondary Sjögren syndrome manifest as keratoconjunctivitis sicca or xerostomia occurs in approximately 10% of patients with RA. RA also appears to increase the risk of developing B-cell lymphoma by two- to fourfold compared with the general population. The risk of lymphoma appears to correlate with high levels of disease activity or the presence of Felty syndrome. Platelet counts in RA are typically elevated in association with the acute-phase response of inflammation. Immune thrombocytopenia is rare.

17. The answer is D.
(Chap. 6) The therapy of RA has changed dramatically in the past two decades with the development of drugs that modify the disease course of RA. Methotrexate is the disease-modifying antirheumatic drug (DMARD) of first choice for treatment of early RA. Other conventional DMARDs include hydroxychloroquine, sulfasalazine, and leflunomide. Leflunomide, an inhibitor of pyrimidine synthesis, is efficacious as a single agent or in combination with methotrexate. Hydroxychloroquine and sulfasalazine are typically reserved for mild disease. The biologic DMARDs have dramatically improved the treatment of RA in the past decade. There are currently five anti–tumor necrosis factor (TNF) agents, including infliximab, approved for use in patients with RA. Rituximab, an anti-CD20 antibody, is approved for refractory RA in combination with methotrexate. It is more efficacious in seropositive than seronegative patients. Other biologics approved for use in RA include anakinra (interleukin [IL]-1 receptor antagonist), abatacept (CD28/CD80/86 antagonist), and tocilizumab (IL-6 antagonist). NSAIDs, including naproxen, were formerly used as core RA therapy.

However, they are now used as adjunctive treatment for symptom management. T ey are not considered DMARDs.

18. T e answer is E.
(Chap. 7) Felty syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in less than 1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. T rombocytopenia is not a characteristic feature of Felty syndrome. It typically occurs in the late stages of severe RA and is more common in whites than other racial groups. T-cell large granular lymphocytic leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often due to drug therapy.

19. T e answer is C.
(Chap. 6) Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. T e most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma. T e risk of developing lymphoma increases if the patient has high levels of disease activity or Felty syndrome.

20. T e answer is D.
(Chap. 7) Acute rheumatic fever is almost universally due to group A streptococcal disease in present time, though virtually all streptococcal disease may be capable of precipitating rheumatic fever. Although skin infections may be associated with rheumatic fever, far and away the most common presentation is with preceding pharyngitis. T ere is a latent period of approximately 3 weeks from an episode of sore throat to presentation of acute rheumatic fever. T e most common manifestations are fever and polyarthritis, with polyarthritis present in 60–75% of cases. Carditis may also be present, although somewhat less frequently (50–60% of cases). Chorea and indolent carditis may have a subacute presentation. Chorea is present in 2–30% of af ected individuals, whereas erythema marginatum and subcutaneous nodules are rare. Sixty percent of patients with acute rheumatic fever progress to rheumatic heart disease with the endocardium, pericardium, and myocardium all potentially involved. All patients with acute rheumatic fever should receive antibiotics sufficient to treat the precipitating group A streptococcal infection.

21. T e answer is D.
(Chap. 7) T is patient has a history suggestive of recurrent bouts of acute rheumatic fever (ARF) with evidence of mitral regurgitation, mitral stenosis, and aortic regurgitation on physical examination. T is and the presence of atrial fibrillation imply severe rheumatic heart disease. Risk factors for this condition include poverty and crowded living conditions. As a result, ARF is considerably more common in the developing world. Daily aspirin is the treatment of choice for the migratory large-joint arthritis and fever that are common manifestations of ARF. Practitioners sometimes use glucocorticoids during acute bouts of carditis to quell inflammation, although this remains a controversial practice and has no role between flares of ARF. Secondary prophylaxis with either daily oral penicillin or, preferably, monthly IM injections is considered the best method to prevent further episodes of ARF and, therefore, prevent further valvular damage. Primary prophylaxis with penicillin on an as-needed basis is equally ef ective for preventing further bouts of carditis. However, most episodes of sore throat are too minor for patients to present to a physician. T erefore, secondary prophylaxis is considered preferable in patients who already have severe valvular disease. Doxycycline is not a first-line agent for group A Streptococcus, the pathogen that incites ARF.

22. T e answer is A.
(Chap. 7) T ere is a latent period of approximately 3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. T e exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. T e most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–60%). T e prevalence of chorea in ARF varies substantially between populations, ranging from less than 2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in less than 5% of cases.

23. T e answer is A.
(Chap. 8) T e prognosis for patients with scleroderma renal disease is poor. In scleroderma renal crisis patients, prompt treatment with an ACE inhibitor may reverse acute renal failure. In recent studies, the initiation of ACE inhibitor therapy resulted in 61% of patients having some degree of renal recovery and

not needing chronic dialysis support. T e survival rate is estimated to be 80–85% at 8 years. Among patients who needed dialysis, when treated with ACE inhibitors, over 50% were able to discontinue dialysis after 3 to 18 months. T erefore, ACE inhibitors should be used even if the patient requires dialysis support.

24. T e answer is C.
(Chap. 8) Virtually every organ can be clinically af ected with systemic sclerosis (SSc). Most patients with SSc can be classified as either limited (lcSSc) or dif use (dcSSc). Although stratification of SSc patients into dif use and limited cutaneous subsets is useful, disease expression is far more complex, and several distinct endophenotypes exist within each subset. In general, pulmonary parenchymal involvement is more common in patients with dcSSc than lcSSc (see **Figure 4**).



FIGURE 4

25. T e answer is E.
(Chap. 8) Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). T is overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. Laboratory evaluation indicates features of inflammation with elevated ESR and hypergammaglobulinemia. Although anti–U1-RNP antibodies are detected in the serum in high titers, SSc-specific autoantibodies are not found. In contrast to SSc, patients with MCTD often show a good response to treatment with glucocorticoids, and the long-term prognosis is better than that of SSc. Anticentromere antibodies are typically associated with lcSSc.

26. T e answer is D.
(Chap. 9) T e patient presented with classic symptoms for Sjögren syndrome including dry mouth and eyes. T is condition may be primary, as in this case, or secondary in association with another connective tissue disease such as scleroderma or rheumatoid arthritis. Many autoantibodies may be demonstrated in the serum of patients with Sjögren syndrome, including antibodies to Ro/SS-A or La/SS-B. Sialometry will demonstrate decreased production of saliva and MRI or magnetic resonance sialography of the major salivary glands may also demonstrate abnormalities. Ocular involvement with decreased tear production is demonstrated by the Schirmer I test. Scl-70 antibody is associated with scleroderma and should not be positive in primary Sjögren syndrome.

27. T e answer is D.
(Chap. 9) Lymphoma is well known to develop specifically in the late stage of Sjögren syndrome. Common manifestations of this malignant condition include persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, and low C4 complement levels. Most of the lymphomas are extranodal, marginal zone B cell, and low grade. Low-grade lymphomas may be detected incidentally during a labial biopsy. Mortality is higher in patients with concurrent B symptoms (fevers, night sweats, and weight loss), a lymph node mass more than 7 cm, and a high or intermediate histologic grade.

28. T e answer is A.
(Chap. 9) Although Sjogren syndrome most commonly af ects the eyes and mouth, there are a number of common extraglandular sites of involvement. T e most common is arthritis or arthralgias that complicate up to 60% of cases. Raynaud phenomenon is the second most common extraglandular site. Lung involvement and vasculitis are found in less than 20% of patients. Lymphoma, although a concerning and highly morbid complication, is relatively rare, af ecting only 6% of Sjögren patients.

29. T e answer is B.
(Chap. 9) Primary Sjögren syndrome is diagnosed if (1) the patient presents with eye and/or mouth dryness, (2) eye tests disclose keratoconjunctivitis sicca, (3) mouth evaluation reveals the classic manifestations of the syndrome, and/or (4) the patient's serum reacts with Ro/SS-A and/or La/SS-B autoantigens. Labial biopsy is needed when the diagnosis is uncertain or to rule out other conditions that may cause dry mouth or eyes or parotid gland enlargement. See **Table 2** for the dif erential diagnosis of Sjögren syndrome.

TABLE 2

DIFFERENTIAL DIAGNOSIS OF SJÖGREN SYNDROME

HIV INFECTION AND SICCA SYNDROME	SJÖGREN SYNDROME	SARCOIDOSIS
Predominant in young males	Predominant in middle-aged women	No age or sex preference
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of autoantibodies	Lack of autoantibodies to Ro/SS-A and/or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and DRw52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV

30. The answer is D.
(Chap. 10) Ankylosing spondylitis is closely correlated with the presence of the histocompatibility antigen HLA-B27. In North American whites, the prevalence of B27 is 7%, but in patients with ankylosing spondylitis, it is 90%. Not all persons with B27 develop ankylosing spondylitis; the disease is only present in 1–6% of B27-positive individuals.

31. The answer is A.
(Chap. 10) Although the most serious spine complication of ankylosing spondylitis is fracture, there are a number of important extra-articular manifestations. Anterior uveitis is the most common, occurring in 40% of patients with ankylosing spondylitis. Inflammatory bowel disease has been reported to be frequently present. Less common complications include aortic insufficiency, third-degree heart block, pulmonary nodules and upper lobe fibrosis, cardiac dysfunction, retroperitoneal fibrosis, prostatitis, and amyloidosis.

32. The answer is B.
(Chap. 10) NSAIDs are the first line of pharmacologic therapy for ankylosing spondylitis, for which this patient has a classic presentation. These agents have been shown to reduce pain and tenderness and increase mobility. There is even some evidence that they slow disease progression. Given their proven efficacy, tolerability, and safety, they remain first-line therapy. Anti–TNF-α agents have been reported to have dramatic effects in ankylosing spondylitis, with infliximab, etanercept, adalimumab, or golimumab having published reports of success. Because of their potential side effects, including serious infections, hypersensitivity reactions, and others, these agents should be reserved for patients failing therapy with NSAIDs.

33. The answer is E.
(Chap. 10) Reactive arthritis refers to an acute, nonpurulent arthritis that occurs after an infection elsewhere in the body. Often presenting with lower joint inflammatory arthritis occurring 1–4 weeks after a diarrheal episode, reactive arthritis may also include uveitis or conjunctivitis, dactylitis, urogenital lesions, and characteristic mucocutaneous lesions such as keratoderma blennorrhagicum. The most common organisms associated with reactive arthritis are Shigella species, although Yersinia, Chlamydia, and, to a much lesser extent, Salmonella and Campylobacter have been described. Although more common in children residing in developing countries, over 400,000 annual cases of Shigella species infections occur in the United States. These infections mostly occur in children 4–11 years old. Most U.S. cases are due to Shigella sonnei, with Shigella flexneri the second most common cause.

34. The answer is E.
(Chap. 10) Whipple disease is a rare chronic bacterial infection of the gastrointestinal tract most commonly affecting middle-aged men. Arthritis is a common early manifestation of the disease, with arthritis predating gastrointestinal symptoms by 5 years or more. Large and small joints may be affected, and sacroiliitis is common. Arthritis is often migratory and lasts several days with spontaneous recovery. Synovial fluid is generally inflammatory, including polymorphonuclear cells. Radiographs rarely show joint erosions, although sacroiliitis may be demonstrated. Diagnosis is often made by polymerase chain reaction amplification of genetic material from Tropheryma whipplei in biopsied material, most commonly the gut.

35. The answer is C.
(Chap. 10) Enthesopathy or enthesitis is the term used to describe inflammation at the site of tendinous or ligamentous insertion into bone. This type of inflammation is seen most frequently in patients with seronegative spondyloarthropathies and various infections, especially viral infections. The other definitions apply to other terms used in the orthopedic and rheumatic examination. Subluxation is the alteration of joint alignment so that articulating surfaces incompletely approximate each other. Synovitis refers to inflammation at the site of tendinous or ligamentous insertion into bone. Inflammation of a saclike

cavity near a joint that decreases friction is the definition of bursitis. Finally, crepitus is a palpable vibratory or crackling sensation elicited with joint motion.

36. The answer is D.
(Chap. 10) Nail changes in the fingers or toes occur in up to 90% of patients with psoriatic arthritis (PsA), compared with 40% of psoriatic patients without arthritis, and pustular psoriasis is said to be associated with more severe arthritis. Several articular features distinguish PsA from other joint disorders; such hallmark features include dactylitis and enthesitis. Dactylitis occurs in more than 30%; enthesitis and tenosynovitis are also common and are probably present in most patients, although often not appreciated on physical examination. Shortening of digits because of underlying osteolysis is particularly characteristic of PsA, and there is a much greater tendency than in RA for both fibrous and bony ankylosis of small joints. Rapid ankylosis of one or more proximal interphalangeal (PIP) joints early in the course of disease is not uncommon. Back and neck pain and stiffness are also common in PsA. Diarrhea is not a feature of PsA (see **Figure 5**).

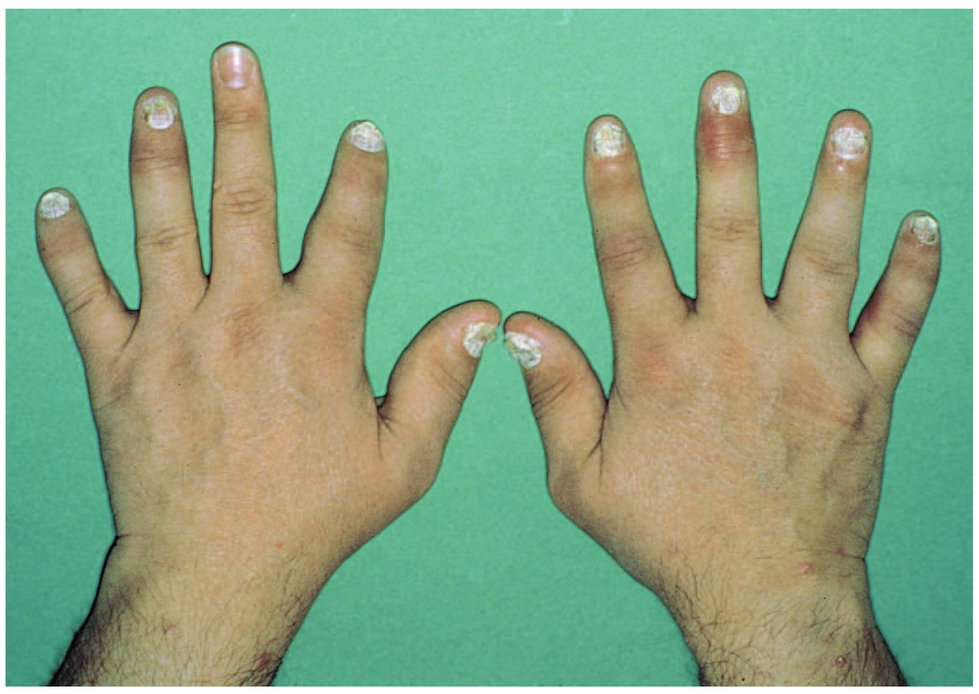


FIGURE 5

37. The answer is A.
(Chap. 10) Aortic insufficiency, sometimes leading to congestive heart failure, occurs in a small percentage of patients, occasionally early. Third-degree heart block may occur alone or together with aortic insufficiency. Subclinical pulmonary lesions and cardiac dysfunction may be relatively common.

38. The answer is B.
(Chap. 11) Although the molecular pathology of most vasculitic syndromes is poorly understood, the deposition of immune complexes is commonly thought to play an important role in vasculitis associated with IgA vasculitis (Henoch-Schönlein), cryoglobulinemic vasculitis associated with hepatitis C, serum sickness, and polyarteritis nodosa–like vasculitis associated with hepatitis B. Granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), and microscopic polyangiitis are associated with antineutrophil cytoplasmic antibodies (ANCA). Pathogenic T-lymphocyte responses are also implicated in granulomatosis with polyangiitis (Wegener's), giant-cell arteritis, Takayasu arteritis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss).

39. The answer is D.
(Chap. 11) The patient presents with classic symptoms for granulomatosis with polyangiitis (Wegener's). The average age of diagnosis is 40 years, and there is a male predominance. Upper respiratory symptoms often predate lung or renal findings and may even present with septal perforation. The diagnosis is made by demonstration of necrotizing granulomatous vasculitis on biopsy. Pulmonary tissue offers the highest yield. Biopsy of the upper airway usually shows the granulomatous inflammation but infrequently shows vasculitis. Renal biopsy may show the presence of pauci-immune glomerulonephritis.

40. The answer is C.
(Chap. 11) The patient has a classic presentation for giant-cell arteritis with associated polymyalgia rheumatica including headache, jaw claudication, and visual disturbances. Her age makes this diagnosis highly likely as well. The diagnosis is confirmed by temporal artery biopsy; however, in the presence of visual symptoms, initiation of therapy should not be delayed pending a biopsy because the biopsy may be positive even after approximately 14 days of glucocorticoid therapy. Delay in therapy risks irreversible visual loss. Additionally, a dramatic response to therapy may lend further support to the diagnosis. The primary therapy is glucocortcoids. Although ESR is nearly universally elevated, it is not specific for the diagnosis. Temporal artery ultrasound may be suggestive but is not diagnostic.

41. The answer is C.
(Chap. 11) The most common manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. The demonstration of circulating cryoprecipitates is a critical component of the diagnosis, and often rheumatoid factor can be found as well. Because hepatitis C infection is present in the vast majority of patients with cryoglobulinemic vasculitis, infection should be sought in all patients with this clinical syndrome.

42. The answer is C.
(Chap. 11) The most likely cause of the acute coronary syndrome in this patient is thrombosis of a coronary artery aneurysm in an individual with a past history of Kawasaki disease. Kawasaki disease is an acute multisystem disease that primarily presents in children less than 5 years of age. The clinical manifestations in childhood are nonsuppurative cervical lymphadenitis; desquamation of the fingertips; and erythema of the oral cavity, lips, and palms. Approximately 25% of cases are associated with coronary artery aneurysms that occur late in illness in the convalescent stage. Early treatment (within 7–10 days of onset) with IV immunoglobulin and high-dose aspirin decreases the risk of developing coronary aneurysms to about 5%. Even if coronary artery aneurysms develop, most regress over the course of the first year if the size is less than 6 mm. Aneurysms more than 8 mm, however, are unlikely to regress. Complications of persistent coronary artery aneurysms include rupture, thrombosis and recanalization, and stenosis at the outflow area. Dissection of the aortic root and coronary ostia is a common cause of death in Marfan syndrome and can also be seen with aortitis due to Takayasu arteritis. In this patient, there is no history of hypertension, limb ischemia, or systemic symptoms that would suggest an active vasculitis. In addition, there are no other ischemic symptoms that would be expected in Takayasu arteritis. Myocardial bridging overlying a coronary artery is seen frequently at autopsy but is an unusual cause of ischemia. The possibility of cocaine use as a cause of myocardial ischemia in a young individual must be considered, but given the clinical history, it is a less likely cause of ischemia in this case.

43. The answer is E.
(Chap. 11) Prior to initiation of azathioprine, thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of azathioprine, should be assayed because inadequate levels may result in severe cytopenia. The antineutrophil cytoplasmic antibody (ANCA) titer can be misleading and should not be used to assess disease activity. Many patients who achieve remission continue to have elevated titers for years. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% of patients relapsed within 1 year of an increase in ANCA levels. Thus, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy.

44. The answer is C.
(Chap. 11) Polyarteritis nodosa does not involve pulmonary arteries, although bronchial vessels may be involved; granulomas, significant eosinophilia, and an allergic diathesis are not observed. Vascular beds typically involved are listed in **Table 3**.

TABLE 3
CLINICAL MANIFESTATIONS RELATED TO ORGAN SYSTEM INVOLVEMENT IN POLYARTERITIS NODOSA

ORGAN SYSTEM	PERCENT INCIDENCE	CLINICAL MANIFESTATIONS
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

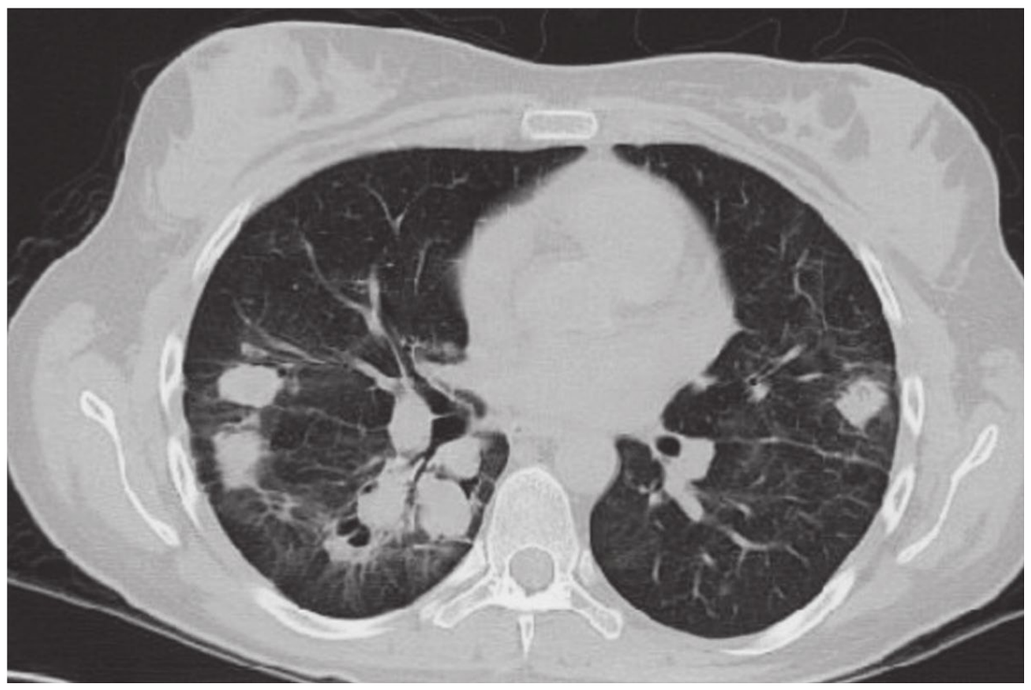
Source: From Cupps TR, Fauci AS: The Vasculitides. Philadelphia, PA: Saunders, 1981.

45. The answer is C.
(Chap. 11) Granulomatosis with polyangiitis (Wegener's) is a small-vessel vasculitis that involves the lung in more than 80% of cases. One-third of patients with radiographic abnormalities may be asymptomatic. It typically also involves the upper respiratory tract and the kidney. Surgical biopsies of radiographically abnormal pulmonary parenchyma have a diagnostic yield of approximately 90% in patients with granulomatosis with polyangiitis (Wegener's). Biopsy may also differentiate vasculitis from infection or malignancy. The yield of bronchoscopic transbronchial biopsy is substantially lower than surgical biopsy. Cryoglobulinemic vasculitis and IgA vasculitis (Henoch-Schönlein) are small-vessel vasculitides that typically involve the skin and kidney. Polyarteritis nodosa is a medium-vessel vasculitis that typically involves the mesenteric vessels. Cutaneous vasculitis represents the most common

vasculitic feature and can be seen in a broad spectrum of settings including infections, medications, malignancies, and connective tissue diseases.

46. The answer is A.
(Chap. 11) In granulomatosis with polyangiitis (Wegener's), 80% of patients may have pulmonary involvement during their disease course. The typical chest radiographic abnormalities are single or multiple nodular infiltrates that often cavitate (**Figures 6A** and **6B**).

Ground glass infiltrates (**Figure 6C**) may occur due to capillaritis and subsequent pulmonary hemorrhage.



A

FIGURE 6A



B

FIGURE 6B



C

FIGURE 6C

Microscopic polyangiitis and SLE are also causes of capillaritis. Patients with granulomatosis with polyangiitis (Wegener's) on immunosuppressive therapy are at risk of opportunistic lung infections. Granulomatosis with polyangiitis (Wegener's) typically will not cause bronchiectasis in the absence of a history of multiple respiratory infections. Bronchiectasis is more typical of cystic fibrosis, ciliary dysfunction syndromes, obstructive lung disease, or congenital immunodeficiency.

47. The answer is C.

(Chap. 12) Recurrent oral ulceration is required for the diagnosis of Behçet's disease. The ulcers may be single or multiple, are shallow based with a yellow necrotic base, and are painful. They are generally small, less than 10 mm in diameter. In addition, the diagnosis of Behçet's disease requires two of the following: recurrent genital ulceration, eye lesions, skin lesions, and pathergy test. Nonspecific skin inflammatory reactivity to any scratches or intradermal saline injection (pathergy test) is common and specific.

48. The answer is A.

(Chap. 12) Behçet's disease is a multisystem disorder of uncertain cause that is marked by oral and genital ulcerations and ocular involvement. It is disorder affects males and females equally and is more common in persons of Mediterranean, Middle Eastern, and Far Eastern descent. Approximately 50% of these persons have circulating autoantibodies to human oral mucosa. The clinical features are quite varied. The presence of recurrent aphthous ulcerations is essential for the diagnosis. Most of these patients have primarily oral ulcerations, although genital ulcerations are more specific for the diagnosis. The ulcers are generally painful, can be shallow or deep, and last for 1 or 2 weeks. Other skin involvement may occur, including folliculitis, erythema nodosum, and vasculitis. Eye involvement is the most dreaded complication because it may progress rapidly to blindness. It often presents as panuveitis, iritis, retinal vessel occlusion, or optic neuritis. This is patient also presents with superficial venous thrombosis. Superficial and deep venous thromboses are present in one-fourth of these patients. Neurologic involvement occurs in up to 10%. Laboratory findings are nonspecific with elevations in the ESR and the white blood cell count. Bullous pemphigoid is a polymorphic autoimmune subepidermal blistering disease usually seen in the elderly. Initial lesions may consist of urticarial plaques; most patients eventually display tense blisters on either normal-appearing or erythematous skin. The lesions are usually distributed over the lower abdomen, groin, and flexor surface of the extremities; oral mucosal lesions are found in some patients. Discoid lupus erythematosus is the cutaneous form of SLE and is characterized by atrophic, depigmented plaques and patches surrounded by hyperpigmentation and erythema in association with scarring and alopecia.

49. The answer is E.

(Chap. 12) Superficial or deep peripheral vein thrombosis is seen in 30% of patients. Pulmonary emboli are a rare complication. The superior vena cava is obstructed occasionally, producing a dramatic clinical picture. Arterial involvement occurs in less than 5% of patients and presents with aortitis or peripheral arterial aneurysm and arterial thrombosis. Pulmonary artery vasculitis presenting with dyspnea, cough, chest pain, hemoptysis, and infiltrates on chest roentgenograms has been reported in 5% of patients and should be differentiated from thromboembolic disease because it warrants anti-inflammatory and not thrombolytic therapy. Neurologic involvement (5%–10%) appears mainly in the parenchymal form (80%); it is associated with brainstem involvement and has a serious prognosis (central nervous system [CNS]-Behçet's disease). IL-6 is persistently raised in cerebrospinal fluid of these patients. Cerebral venous thrombosis is most frequently observed in the superior sagittal and transverse sinuses and is associated with headache and increased intracranial pressure. MRI and/or proton magnetic resonance spectroscopy are very sensitive and should be employed if CNS-Behçet's disease is suspected. Gastrointestinal involvement is seen more frequently in patients from Japan and consists of mucosal ulcerations of the gut, resembling Crohn disease. Epididymitis is seen in 5% of patients, whereas amyloidosis of AA type and glomerulonephritis are uncommon.

50. The answer is B.

(Chap. 17) When patients present with proximal muscle weakness and myositis, whether polymyositis, dermatomyositis, or inclusion body myositis, the diagnosis is confirmed by analysis of serum muscle enzymes, electromyography (EMG) findings, and muscle biopsy. The most sensitive serum enzyme is creatinine kinase (CK), which can be elevated as much as 50-fold in active disease. CK levels usually parallel disease activity, but can be normal in some patients with inclusion body myositis or dermatomyositis.

CK is always elevated in active polymyositis and thus is considered most sensitive. Other enzymes may be elevated as well, including glutamic-oxaloacetic transaminase, glutamate pyruvate transaminase, lactate dehydrogenase, and aldolase.

51. T e answer is C.

(Chap. 17) Various autoantibodies against nuclear antigens (e.g., ANA) and cytoplasmic antigens are found in up to 20% of patients with inflammatory myopathies. T e antibodies to cytoplasmic antigens are directed against ribonucleoproteins involved in protein synthesis (antisynthetases) or translational transport (anti–signal-recognition particles). T e antibody directed against the histidyl-transfer RNA synthetase, called anti-Jo-1, accounts for 75% of all the antisynthetases and is clinically useful because up to 80% of patients with this autoantibody will have interstitial lung disease. Patients with anti-Jo-1 may also have Raynaud phenomenon, nonerosive arthritis, and the MHC molecules DR3 and DRw52. Interstitial lung disease associated with anti-Jo-1 is often rapidly progressive and fatal, even if treated aggressively with cyclophosphamide or other immunosuppressants.

52. T e answer is A.

(Chap. 17) Dermatomyositis is associated with malignancy in up to 15% of cases; thus, age-appropriate cancer screening is indicated when this diagnosis is made. Exhaustive cancer searches are not recommended, however. Dermatomyositis may be associated occasionally with scleroderma and mixed connective tissue disease, but less frequently with SLE, RA, or Sjögren syndrome, which are more closely associated with polymyositis or inclusion body myositis (IBM). Viruses may be associated with IBM and polymyositis but are not proven to be associated with dermatomyositis. Parasites and bacteria such as cestodes and nematodes are associated with polymyositis, but not other forms of inflammatory myopathy. Finally, thyroid-stimulating immunoglobulins are not known to be associated with dermatomyositis.

53. T e answer is A.

(Chap. 17) Mild statin-induced myopathy is noninflammatory and usually resolves with discontinuation of therapy. In rare patients, however, muscle weakness continues to progress even after the statin is withdrawn; in these cases, a diagnostic muscle biopsy is indicated and search for antibodies to 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR) is suggested; if histologic evidence of polymyositis or necrotizing myositis is present, immunotherapy should be initiated. ANA may be present but is nonspecific in these cases. Anti-Jo-1 antibodies are associated with the antisynthetase syndromes where myositis is usually accompanied by interstitial lung disease and stereotypical skin changes. Antibodies against signal recognition particle (SRP) are not associated with statin-induced myopathy.

54. T e answer is E.

(Chap. 13) Relapsing polychondritis most often presents with recurrent painful swelling of the ear. Although other cartilaginous sites may be involved such as the nose and the tracheobronchial tree, these are less frequent. Episodes of ear involvement may result in floppy ears. Typically the pinna is af ected while the earlobe is spared because there is no cartilage in the lobe. Cogan's syndrome is a rare vasculitic syndrome involving hearing loss, but cartilage inflammation is not a feature. Recurrent trauma or irritation is a consideration, but the history is not suggestive, and it would less likely be bilateral and accompanied by inflammatory findings and a relatively spared earlobe.

55. T e answer is E.

(Chap. 14) Despite multiple investigations, the cause of sarcoidosis remains unknown. Currently, the most likely etiology is an infectious or noninfectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Among the possible infectious agents, careful studies have shown a much higher incidence of Propionibacterium acnes in the lymph nodes of sarcoidosis patients compared to controls. An animal model has shown that P acnes can induce a granulomatous response in mice similar to sarcoidosis. Others have demonstrated the presence of a mycobacterial protein (Mycobacterium tuberculosis catalase-peroxidase [mKatG]) in the granulomas of some sarcoidosis patients. T is protein is very resistant to degradation and may represent the persistent antigen in sarcoidosis. Immune response to this and other mycobacterial proteins has been documented by another laboratory. T ese studies suggest that a Mycobacterium similar to M tuberculosis could be responsible for sarcoidosis. T e mechanism of exposure/infection with such agents has been the focus of other studies. Environmental exposures to insecticides and mold have been associated with an increased risk for disease. In addition, healthcare workers appear to have an increased risk. Also, sarcoidosis in a donor organ has occurred after

transplantation into a sarcoidosis patient. Some authors have suggested that sarcoidosis is not due to a single agent but represents a particular host response to multiple agents. Some studies have been able to correlate the environmental exposures to genetic markers. T ese studies have supported the hypothesis that a genetically susceptible host is a key factor in the disease. Although helper T cells may be increased, particularly in the lung of patients with sarcoidosis, it is not a monoclonal or malignant expansion of cells.

56. T e answer is D.
(Chap. 14) Lung involvement occurs in more than 90% of sarcoidosis patients and is by far the most common manifestation of sarcoidosis. Characteristic computed tomography (CT) features include peribronchial thickening and reticular nodular changes, which are predominantly subpleural. T e peribronchial thickening seen on CT scan seems to explain the high yield of granulomas from bronchial biopsies performed for diagnosis. Usually the infiltrates in sarcoidosis are predominantly an upper lobe process. Approximately one-half of sarcoidosis patients present with obstructive disease, reflected by a reduced ratio of forced expiratory volume in 1 second to forced vital capacity. Cough is a common symptom. Airway involvement causing varying degrees of obstruction underlies the cough in most sarcoidosis patients. Pulmonary arterial hypertension is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension. In sarcoidosis patients with end-stage fibrosis awaiting lung transplant, 70% will have pulmonary arterial hypertension. T is is a much higher incidence than that reported for other fibrotic lung diseases. In less advanced, but still symptomatic, patients, pulmonary arterial hypertension has been noted in up to 50% of the cases. Because sarcoidosis-associated pulmonary arterial hypertension may respond to therapy, evaluation for this should be considered in persistently dyspneic patients.

57. T e answer is D.
(Chap. 14) Hypercalcemia and/or hypercalciuria occurs in about 10% of sarcoidosis patients. It is more common in whites than African Americans and in men. T e mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself. T e 1,25-dihydroxyvitamin D causes increased intestinal absorption of calcium, leading to hypercalcemia with a suppressed parathyroid hormone (PTH) level. Increased exogenous vitamin D from diet or sunlight exposure may exacerbate this problem. Serum calcium should be determined as part of the initial evaluation of all sarcoidosis patients, and a repeat determination may be useful during the summer months with increased sun exposure.

58. T e answer is C.
(Chap. 14) T e presence of cardiac involvement is influenced by race. Although over a quarter of Japanese sarcoidosis patients develop cardiac disease, only 5% of sarcoidosis patients in the United States and Europe develop symptomatic cardiac disease. However, there is no apparent racial predilection between whites and African Americans.

59. T e answer is E.
(Chap. 14) Cardiac sarcoidosis classically presents as either congestive heart failure or cardiac arrhythmias, which results from infiltration of the heart muscle by granulomas. Valvular, coronary, or pericardial involvement with granulomatous disease has also been described. Dif use granulomatous involvement of the heart muscle can lead to profound dysfunction with left ventricular ejection fractions below 10%. Even in this situation, improvement in the ejection fraction can occur with systemic therapy. Arrhythmias can also occur with dif use infiltration or with more patchy cardiac involvement. If the atrioventricular node is infiltrated, heart block can occur, which can be detected by routine electrocardiography. Ventricular arrhythmias and sudden death due to ventricular tachycardia are common causes of death. Arrhythmias are best detected using 24-hour ambulatory monitoring, and electrophysiology studies may be negative. Other screening tests for cardiac disease include routine electrocardiography and echocardiography. T e confirmation of cardiac sarcoidosis is usually performed with either MRI or positron emission tomography (PET) scanning.

60. T e answer is D.
(Chap. 15) T is patient has IgG4-related disease (IgG4-RD). IgG4-RD is a fibroinflammatory condition characterized by a tendency to form tumefactive lesions. T e clinical manifestations of this disease, however, are protean and continue to be defined. Pancreatic and retroperitoneal involvement is well described and may present as type 1 autoimmune pancreatitis, presenting as mild abdominal pain,

weight loss, and acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass). Imaging shows dif use (termed sausage-shaped pancreas) or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy. T e key histopathology characteristics of IgG4-RD are a dense lymphoplasmacytic infiltrate that is organized in a storiform pattern (resembling a basket weave), obliterative phlebitis, and a mild to moderate eosinophilic infiltrate. T e inflammatory infiltrate is composed of an admixture of B and T lymphocytes. B cells are typically organized in germinal centers. Plasma cells staining for CD19, CD138, and IgG4 appear to radiate out from the germinal centers. Vital organ involvement must be treated aggressively, however, because IgG4-RD can lead to serious organ dysfunction and failure. Aggressive disease can lead quickly to end-stage liver disease, permanent impairment of pancreatic function, renal atrophy, aortic dissection or aneurysms, and destructive lesions in the sinuses and nasopharynx. Glucocorticoids are the first line of therapy. Treatment regimens, extrapolated from experience with the management of autoimmune pancreatitis, generally begin with 40 mg/d of prednisone, with tapering to discontinuation or maintenance doses of 5 mg/d within 2 or 3 months. T e clinical response to glucocorticoids is usually swift and striking; however, longitudinal data indicate that disease flares occur in more than 90% of patients within 3 years. Conventional glucocorticoid-sparing agents such as azathioprine and mycophenolate mofetil have been used in some patients; however, evidence for their efficacy is lacking.

61. T e answer is A.

(Chap. 16) Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation. T e FMF gene encodes a 781-amino acid, approximately 95-kDa protein denoted pyrin (or marenostrin) that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. Typical FMF episodes generally last 24–72 hours, with arthritic attacks tending to last somewhat longer. In some patients, the episodes occur with great regularity, but more often, the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission.

If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children. Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distention with mild tenderness on direct palpation to severe generalized pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. CT scanning may demonstrate a small amount of fluid in the abdominal cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare. Exercise-induced (nonfebrile) myalgia is common in FMF, and a small percentage of patients develop a protracted febrile myalgia that can last several weeks.

62. T e answer is A.

(Chap. 16) T e treatment of choice for FMF is daily oral colchicine, which decreases the frequency and intensity of attacks and prevents the development of amyloidosis in compliant patients. Intermittent dosing at the onset of attacks is not as ef ective as daily prophylaxis and is of unproven value in preventing amyloidosis. T e usual adult dose of colchicine is 1.2–1.8 mg/d, which causes substantial reduction in symptoms in two-thirds of patients and some improvement in more than 90%. Children may require lower doses, although not proportionately to body weight.

63. T e answer is E.

(Chap. 19) Osteoarthritis (OA) af ects certain joints, yet spares others. Commonly, af ected joints include the cervical and lumbosacral spine, hip, knee, and first metatarsal phalangeal joint (MTP). In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often af ected. Usually spared are the wrist, elbow, and ankle. Human joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips). Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses (see **Figure 7**).

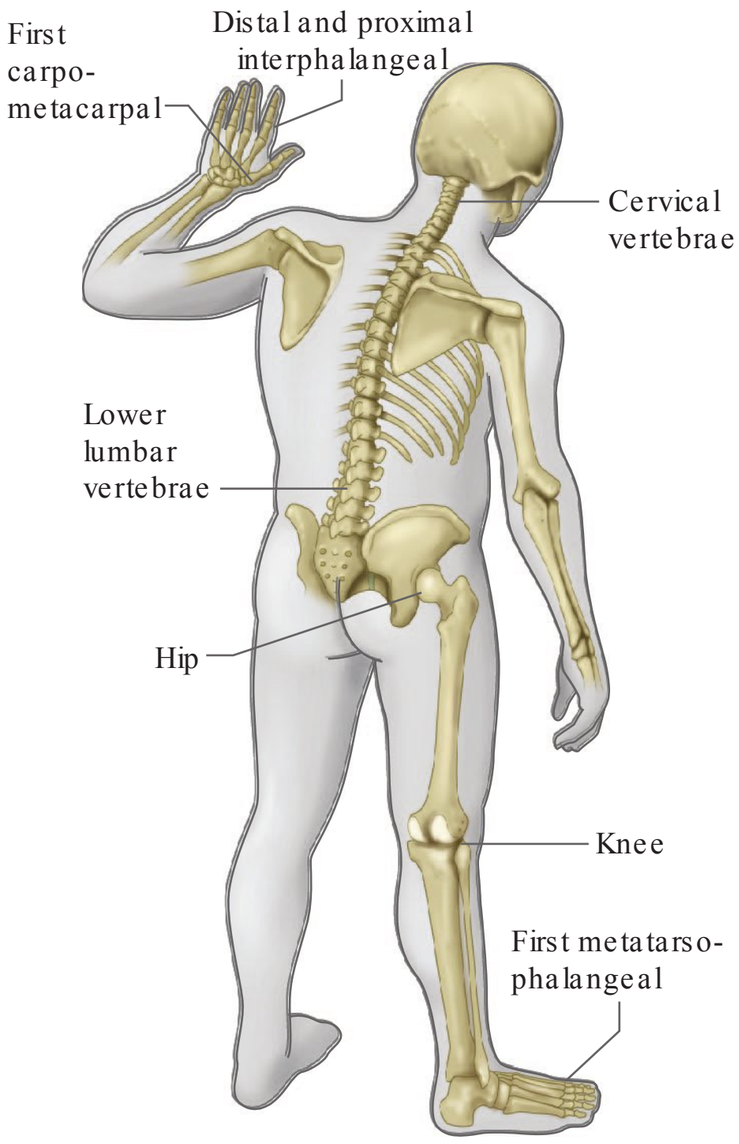


FIGURE 7

64. The answer is D.

(Chap. 19) Examination of the synovial fluid is often helpful in suspected osteoarthritis, particularly if inflammatory disease is possible. If the synovial fluid white blood cell count is more than 1000/μL, inflammatory arthritis, gout, or pseudogout is likely, with the latter two being also identified by the presence of crystals. Because cartilage is aneural, cartilage loss in a joint is not accompanied by pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by the x-ray, and the severity of radiographic changes in OA correlates poorly with pain severity. OA is the most common type of arthritis. Its high prevalence, especially in the elderly, and the high rate of disability related to disease make it a leading cause of disability in the elderly. Although MRI may reveal the extent of pathology in an osteoarthritic joint, it is not indicated as part of the diagnostic workup.

65. The answer is C.

(Chap. 19) Recent guidelines recommend against the use of glucosamine or chondroitin for OA. Large publicly supported trials have failed to show that, compared with placebo, these compounds relieve pain in persons with disease. Glucocorticoid injections are efficacious in OA, but response is variable, with some patients having little relief of pain, whereas others experience pain relief lasting several months. Glucocorticoid injections are useful to get patients over acute flares of pain and may be especially indicated if the patient has coexistent OA and crystal deposition disease, especially from calcium pyrophosphate dihydrate crystals. Acetaminophen (paracetamol) is the initial analgesic of choice for patients with OA in knees, hips, or hands. For some patients, it is adequate to control symptoms, in which case more toxic drugs such as NSAIDs can be avoided. Doses up to 1 g three times daily can be used. NSAIDs are the most popular drugs to treat osteoarthritic pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produced approximately 30% greater improvement in pain than high-dose acetaminophen. Ultimately, when the patient with knee or hip OA has failed medical treatment modalities and remains in pain, with limitations of physical function that compromise the quality of life, the patient should be referred for total knee or hip arthroplasty. These are highly efficacious operations that relieve pain and improve function in the vast majority of patients, although rates of success are higher for hip than knee replacement.

66. The answer is E.

(Chap. 20) **Figure 8** illustrates extracellular and intracellular monosodium urate crystals, as seen in a fresh preparation of synovial fluid. This is gout. Most patients with gout are overproducers of uric acid. Hyaline cartilage degeneration is typical of osteoarthritis, which usually has a bland synovial aspirate. Antibodies to ANA are typical of lupus, rare in an

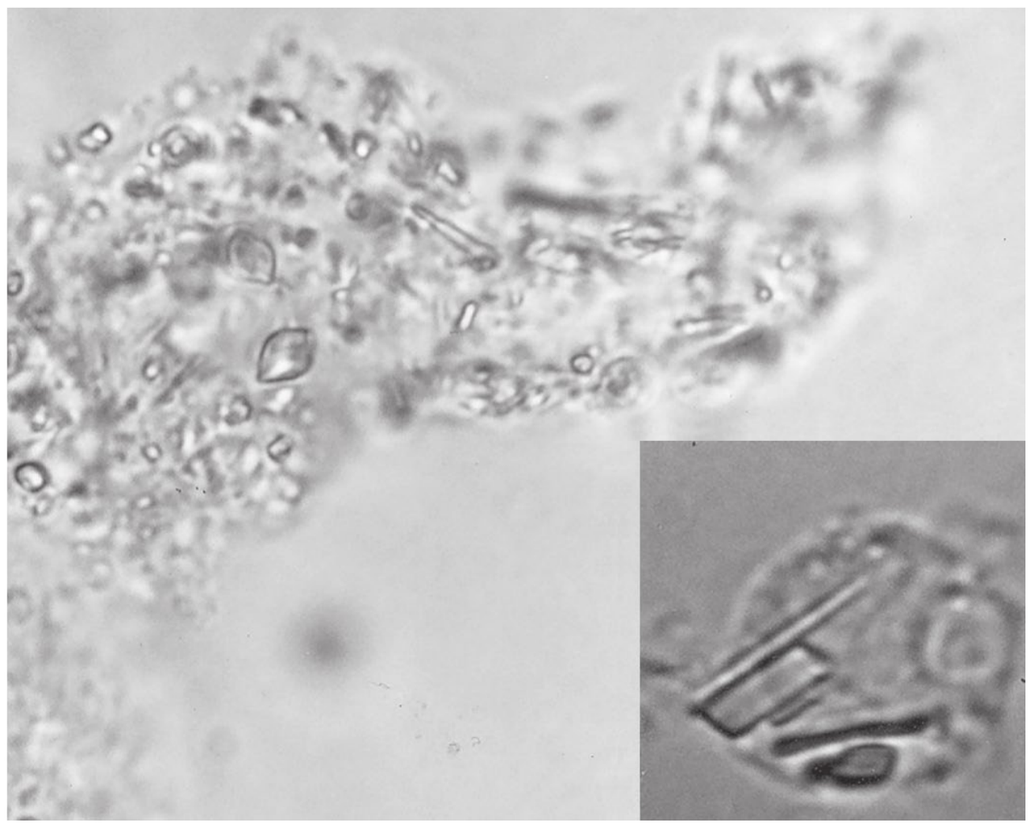


FIGURE 8

elderly man, and not associated with crystalline fluid. Bacterial joint infection would have a purulent synovial fluid. Increased production of inorganic pyrophosphate is a cause of calcium pyrophosphate deposition disease (CPPD; pseudogout), another crystalline arthropathy. CPPD crystals are shown in Figure 8.

67. The answer is C.

(Chap. 20) The xanthine oxidase inhibitor allopurinol is by far the most commonly used hypouricemic agent and is the best drug to lower serum urate in overproducers, urate stone formers, and patients with renal disease. It can be given in a single morning dose, usually 100 mg initially and increasing up to 800 mg if needed. In patients with chronic renal disease, the initial allopurinol dose should be lower and adjusted depending on the serum creatinine concentration; for example, with a creatinine clearance of 10 mL/min, one generally would use 100 mg every other day. Doses can be increased gradually to reach the target urate level of less than 6 mg/dL. Toxicity of allopurinol has been recognized increasingly in patients who use thiazide diuretics, in patients allergic to penicillin and ampicillin, and in Asians expressing HLA-B*5801. Colchicine is commonly used with allopurinol in the treatment of gout. Allopurinol and azathioprine should not be coprescribed because azathioprine can greatly increase blood levels of allopurinol and lead to toxicity.

68. The answer is C.

(Chap. 22) This patient presents with a characteristic history for fibromyalgia, a diffuse pain syndrome associated with increased sensitivity to evoked pain. The underlying pathophysiology of pain in fibromyalgia is felt to be related to altered pain processing in the central nervous system. Epidemiologically, women are affected nine times more frequently than men. The worldwide prevalence of fibromyalgia is 2–3%, but in primary care practices, it is as high as 5–10%. The disorder is even more common in patients with degenerative or inflammatory rheumatic disorders, with a prevalence of 20% or higher. The most common presenting complaint is diffuse pain that is difficult to localize. Pain is both above and below the waist and affects the extremities as well as the axial skeleton. However, it does not localize to a specific joint. The pain is noted to be severe in intensity and difficult to ignore and interferes with daily functioning. Although this patient demonstrates pain at several tender points, the American College of Rheumatology no longer includes tender point assessment in the diagnostic criteria for fibromyalgia. Rather, the new criteria focus on clinical symptoms of widespread pain and neuropsychological symptoms that have been present for at least 3 months. Some of the neuropsychological conditions that are frequently observed in fibromyalgia include sleep disturbance, impaired cognitive functioning, fatigue, stiffness, anxiety, and depression. The lifetime prevalence of mood disorders in patients with fibromyalgia is 80%. Sleep disturbances can include difficulty falling asleep, difficulty staying asleep, or nonrestorative sleep, among others.

69. The answer is D.

(Chap. 22) Fibromyalgia is a common disorder affecting 2–5% of the population. It presents as a diffuse pain syndrome with associated neuropsychological symptoms including depression, anxiety, fatigue, cognitive dysfunction, and disturbed sleep. Treatment for fibromyalgia should include a combination of nonpharmacologic and pharmacologic approaches. Patient education regarding the disease is important to provide a framework for understanding symptoms. The focus of treatment should not be on eliminating pain, but rather improving function and quality of life. Physical conditioning is an important part of improving function and should include a multifaceted exercise program with aerobic exercise, strength training, and exercises that incorporate relaxation techniques such as yoga or tai chi. Cognitive behavioral therapy can be useful in improving sleep disturbance and also for decreasing illness behaviors. Pharmacologic therapy in fibromyalgia is targeted at the afferent and efferent pain pathways. The two most common categories of medications for fibromyalgia are antidepressants and anticonvulsants. Amitriptyline, duloxetine, and milnacipran have all been used with some efficacy in fibromyalgia. Duloxetine and milnacipran are approved by the U.S. Food and Drug Administration (FDA) for the treatment of fibromyalgia. The anticonvulsants that are predominantly used in fibromyalgia are those that are ligands of the α-2-δ subunit of voltage-gated calcium channels. These include gabapentin and pregabalin, which is also FDA approved for treatment of fibromyalgia. Anti-inflammatory medications and glucocorticoids are not effective in fibromyalgia. However, if there is a comorbid triggering condition such as RA, appropriate therapy directed at the underlying disorder is critical to controlling symptoms of fibromyalgia as well. Opioid analgesics such as oxycodone should be avoided. They have no efficacy in treating fibromyalgia and may induce hyperalgesia that can worsen both pain and function.

70. T e answer is A.

(Chap. 22) Fibromyalgia is characterized by chronic widespread musculoskeletal pain, stif ness, paresthesia, disturbed sleep, and easy fatigability. It occurs in a 9:1 female-to-male ratio. It is not confined to any particular region, ethnicity, or climate. Although the pathogenesis is not clear, there are associations with disturbed sleep and abnormal pain perception. Fibromyalgia is diagnosed by the presence of widespread pain, a history of widespread musculoskeletal pain that has been present for more than 3 months, and presence of neuropsychological dysfunction (fatigue, waking unrefreshed, or cognitive symptoms). In the prior diagnostic criteria, it was required to demonstrate pain on palpation at 11 of 18 tender point sites. However, this was abandoned in the updated criteria because it was felt that strict application of a threshold of pain could lead to underdiagnosis of the disorder. Besides pain on palpation, the neurologic and musculoskeletal examinations are normal in patients with fibromyalgia. Psychiatric illnesses, particularly depression and anxiety disorders, are common comorbidities in these patients but do not help satisfy any diagnostic criteria.

71. T e answer is A.

(Chap. 23) T e finding shown in Figure 3 is characteristic of clubbing. Clubbing occurs in the distal portions of the digits and is characterized by widening of the fingertips, convexity of the nail contour, and loss of the normal 15-degree angle between the proximal nail and cuticle. Clinically, it can be sometimes difficult to ascertain whether clubbing is present. One approach to the diagnosis of clubbing is to measure the diameter of the finger at the base of the nail and at the tip of the finger in all 10 fingers. For each finger, a ratio between the base of the nail and the tip of the finger is determined. If the sum of all 10 fingers is greater than 1, then clubbing is felt to be present. A simpler approach is to have an individual place the dorsal surfaces of the distal fourth digits from each hand together. In a normal individual, there should be a diamond-shaped space between the digits. When an individual has clubbing, this space is obliterated. Clubbing most commonly occurs in advanced lung disease, especially bronchiectasis, cystic fibrosis, and interstitial lung diseases like sarcoidosis or idiopathic pulmonary fibrosis. Clubbing was originally described in individuals with empyema and can occur in chronic lung infections, including lung abscess, tuberculosis, or fungal infections. Pulmonary vascular lesions and lung cancer also are associated with clubbing. However, chronic obstructive pulmonary disease does not cause clubbing. However, the causes of clubbing are not limited to the pulmonary system alone. Clubbing can be a benign familial condition and is also associated with a variety of other disorders, including cyanotic congenital heart disease, subacute bacterial endocarditis, Crohn disease, ulcerative colitis, celiac disease, and cancer of the esophagus, liver, small bowel, and large bowel. In untreated hyperthyroidism, clubbing can occur in association with periostitis in a condition called thyroid acropachy. Although these numerous clinical associations have been described for many centuries, the cause of clubbing remains unknown.

72. T e answer is C.

(Chap. 23) Symptoms of hemochromatosis usually begin between the ages of 40 and 60 but can appear earlier. Arthropathy, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. T e arthropathy is an osteoarthritis-like disorder af ecting the small joints of the hands and later the larger joints, such as knees, ankles, shoulders, and hips. T e second and third metacarpophalangeal joints of both hands are often the first and most prominent joints af ected; this clinical picture may provide an important clue to the possibility of hemochromatosis because these joints are not predominantly af ected by "routine" osteoarthritis. Patients experience some morning stif ness and pain with use of involved joints. T e af ected joints are enlarged and mildly tender. Radiographs show narrowing of the joint space, subchondral sclerosis, subchondral cysts, and juxta-articular proliferation of bone. Hooklike osteophytes are seen in up to 20% of patients; although they are regarded as a characteristic feature of hemochromatosis, they can also occur in osteoarthritis and are not disease specific. Bony erosions are typical of rheumatoid arthritis, not hemochromatosis. T e synovial fluid is noninflammatory. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease, and some patients experience episodes of acute pseudogout late in the course of disease (Chap. 20). T e treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little ef ect on established arthritis, which, along with chondrocalcinosis, may progress. Symptom-based treatment of the arthritis consists of administration of acetaminophen and NSAIDs, as tolerated. Acute pseudogout attacks are treated with high doses of an NSAID or a short course of glucocorticoids.

Hip or knee total joint replacement has been successful in advanced disease.

73. T e answer is E.

(Chap. 24) Trochanteric bursitis is a common cause of hip pain and results from inflammation within the bursa that surrounds the insertion of the gluteus medius onto the greater trochanter of the femur. Bursae lie throughout the body with the purpose of facilitating movement of tendons and muscles over bony prominences. Bursitis has many causes, including overuse, trauma, systemic disease, or infection. Trochanteric bursitis typically presents with acute or subacute hip pain with a varying quality. T e pain localizes to the lateral aspect of the hip and upper thigh. Direct palpation over the posterior aspect of the greater trochanter reproduces the pain, and often sleeping on the af ected side is painful. Pain is also elicited with external rotation and resisted abduction of the hip. Treatment of trochanteric bursitis includes use of NSAIDs and avoidance of overuse. If the pain persists, glucocorticoid injection into the af ected bursa may be beneficial.

Other causes of hip pain include osteoarthritis, avascular necrosis, meralgia paresthetica, septic arthritis, occult hip fracture, and referred pain from lumbar spine disease. In patients with true disorders of the hip joint such as osteoarthritis, avascular necrosis, and occult hip fracture, the pain is most commonly localized to the groin area. Meralgia paresthetica (lateral femoral nerve entrapment syndrome) causes a neuropathic pain in the upper outer thigh with symptoms ranging from tingling sensations to a burning pain. When degenerative spinal disease is the cause of referred hip pain, there is typically back pain as well. In addition, palpation over the lateral joint would not reproduce the pain. Iliotibial band syndrome causes lateral knee pain but not hip pain.

74. T e answer is B.

(Chap. 24) T e iliotibial band is comprised of thick connective tissue that runs along the outer thigh from the ilium to the fibula. When this band becomes tightened or inflamed, pain most commonly occurs where the band passes over the lateral femoral condyle of the knee, leading to a burning or aching pain in this area that can radiate toward the outer thigh. T is overuse injury is most often seen in runners and can be caused by improperly fitted shoes, running on uneven surfaces, and excessive running. It is also more common in individuals with a varus alignment of the knee (bowlegged). Treatment of iliotibial band syndrome involves rest, NSAIDs, physical therapy, and addressing risk factors such as poorly fitted shoes or uneven running surface. Glucocorticoid injection at the lateral femoral condyle may alleviate pain, but running must strictly be avoided for 2 weeks following injection. In refractory cases, surgical release of the iliotibial band may be beneficial.

75. T e answer is A.

(Chap. 24) Adhesive capsulitis is characterized by pain and restricted motion of the shoulder. Usually this occurs in the absence of intrinsic shoulder disease, including osteoarthritis and avascular necrosis. It is, however, more common in patients who have had bursitis or tendinitis previously as well as patients with other systemic illnesses, such as chronic pulmonary disease, ischemic heart disease, and diabetes mellitus. T e etiology is not clear, but adhesive capsulitis appears to develop in the setting of prolonged immobility. Reflex sympathetic dystrophy may also occur in the setting of adhesive capsulitis. Clinically, this disorder is more commonly seen in females over age 50. Pain and stif ness develop over the course of months to years. On physical examination, the af ected joint is tender to palpation, with a restricted range of motion. T e gold standard for diagnosis is arthrography with limitation of the amount of injectable contrast to less than 15 mL. In most patients, adhesive capsulitis will regress spontaneously within 1 to 3 years. NSAIDs, glucocorticoid injections, physical therapy, and early mobilization of the arm are useful therapies.

76. T e answer is B.

(Chap. 24) Inflammation of the abductor pollicis longus and the extensor pollicis brevis at the radial styloid process tendon sheath is known as De Quervain tenosynovitis. Repetitive twisting of the wrist can lead to this condition. Pain occurs when grasping with the thumb and can extend radially along the wrist to the radial styloid process. Mothers often develop this tenosynovitis by holding their babies with the thumb outstretched. T e Finkelstein sign is positive in De Quervain tenosynovitis. It is positive if the patient develops pain by placing the thumb in the palm, closing the fingers around the thumb, and deviating the wrist in the ulnar direction. Management of De Quervain tenosynovitis includes NSAIDs and splinting. Glucocorticoid injections can be ef ective. A Phalen maneuver is used to diagnose carpal tunnel syndrome and does not elicit pain. T e wrists are flexed

for 60 seconds to compress the median nerve to elicit numbness, burning, or tingling. Gouty arthritis will present with an acutely inflamed joint with crystal-laden fluid. Rheumatoid arthritis is a systemic illness with characteristic joint synovitis and radiographic features.

77. The answer is C.

(Chap. 24) This patient has plantar fasciitis, a diagnosis that often can be made clinically. It is a common cause of foot pain in adults, with the peak incidence occurring in people between the ages of 40 and 60 years. The pain originates at or near the site of the plantar fascia attachment to the medial tuberosity of the calcaneus. Several factors that increase the risk of developing plantar fasciitis include obesity, pes planus (flat foot or absence of the foot arch when standing), pes cavus (high-arched foot), limited dorsiflexion of the ankle, prolonged standing, walking on hard surfaces, and faulty shoes. In runners, excessive running and a change to a harder running surface may precipitate plantar fasciitis. Smoking and oral contraceptives are not specific risk factors. Patients experience severe pain with the first steps on arising in the morning or following inactivity during the day. The pain usually lessens with weight-bearing activity during the day, only to worsen with continued activity. Pain is made worse on walking barefoot or up stairs. On examination, maximal tenderness is elicited on palpation over the inferior heel corresponding to the site of attachment of the plantar fascia. Imaging studies may be indicated when the diagnosis is not clear. Plain radiographs may show heel spurs, which are of little diagnostic significance. Ultrasonography in plantar fasciitis can demonstrate thickening of the fascia and diffuse hypoechogenicity, indicating edema at the attachment of the plantar fascia to the calcaneus. MRI is a sensitive method for detecting plantar fasciitis, but it is usually not required for establishing the diagnosis. The differential diagnosis of inferior heel pain includes calcaneal stress fractures, the spondyloarthritides, rheumatoid arthritis, gout, neoplastic or infiltrative bone processes, and nerve compression/entrapment syndromes.

Resolution of plantar fasciitis symptoms occurs within 12 months in more than 80% of patients. Initial treatment consists of ice, heat, massage, and stretching. Orthotics providing medial arch support can be effective. A short course of NSAIDs can be given to patients when the benefits outweigh the risks. Local glucocorticoid injections have also been shown to be efficacious but may carry an increased risk for plantar fascia rupture. Plantar fasciotomy is reserved for those patients who have failed to improve after at least 6–12 months of conservative treatment.

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